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HUMAN BIOLOGY

a record of research

DECEMBER, 1946

Vol. 18 No 4

PUBLISHED QUARTERLY BY
THE JOHNS HOPKINS PRESS, BALTIMORE, MARYLAND, U.S.A.

HUMAN BIOLOGY

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HUMAN BIOLOGY is published quarterly by The Johns Hopkins Press, Baltimore, Maryland, U. S. A. The advance subscription price is $5.00 a year (foreign postage 35 cents; Canadian 13 cents). Single current issues are $2.00 each; back numbers, $3.00 each; back volumes, $6.00; plus postage. Subscriptions for less than a year are charged at the single issue price.

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THE JOHNS HOPKINS PRESS, *Publishers*
BALTIMORE—5, MARYLAND, U. S. A.

Entered as Second Class matter, February 18, 1929, at the Post Office at Baltimore, Md., under the Act of March 3, 1879.

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CHEMOPROPHYLAXIS IN THE PREVENTION OF DISEASE WITH ESPECIAL REFERENCE TO MENINGOCOCCAL INFECTIONS[1]

I. A COMPARATIVE STUDY OF THE ABSORPTION, PERSISTENCE AND EXCRETION OF FOUR SULFONAMIDE COMPOUNDS

BY JOHN J. PHAIR,[2] EMANUEL B. SCHOENBACH,[3] AND MARGARET MERRELL[4]

SMALL doses of the sulfonamides have been advocated recently for the prophylaxis of selected bacterial infections. This application of chemotherapy at sub-therapeutic dosage has been employed chiefly among controlled populations such as institutional groups or units of the armed forces. The success of this procedure depends primarily upon knowledge of the epidemiology

[1] From the Department of Epidemiology and the Department of Biostatistics (Paper No. 230), School of Hygiene and Public Health, The Johns Hopkins University. These investigations were aided by the Commission on Meningococcal Meningitis, Board for the Investigation and Control of Influenza and Other Epidemic Diseases, Preventive Medicine Service, Office of the Surgeon General, War Department, Washington, D. C.

The authors gratefully acknowledge their indebtedness to Dr. Kenneth F. Maxcy, Professor of Epidemiology, and Dr. Lowell J. Reed, Professor of Biostatistics, School of Hygiene and Public Health, The Johns Hopkins University, for valuable criticism, suggestions and advice in the preparation of this manuscript. This investigation received invaluable support through the cooperation of Maj.

of the disease in question, the specific drug sensitivity of the parasite, the pharmacology of the various effective compounds and inversely on the associated hazard. The objectives of the program should be clearly defined and the procedure so arranged that undesirable sequelae such as interference with the normal activities of the treated group, untoward reactions of drug sensitive individuals, subsequent sensitization of others, and the *in vivo* selection of relatively drug resistant variants of the parasite are avoided or minimized.

The Commission on Meningococcal Meningitis of the Army Epidemiological Board has been concerned with the problems of chemoprophylaxis in the control of meningococcal infections and a series of investigations of the subject was instituted. One of these, the comparative behavior of sulfonamides with regard to absorption, persistence and excretion, when administered to troops, will be discussed in detail in this report.

The sulfonamides studied in this investigation were sulfanilamide, sulfadiazine, sulfamerazine, and sulfamethazine, and the experiment was so arranged as to allow reasonably accurate determinations of rates of absorption and elimination of the free drug, as well as a measurement of the persistence of the drug in the blood stream, during the 24 hours following ingestion of one or two grams as a single dose.

A number of studies have been reported in the literature showing differences in blood concentrations of certain of these compounds but either inadequate control of some of the important variables or a limitation in the number and dosage of the drugs compared, rendered them unsuitable for deriving the rate constants and other quantitative relationships of the sulfonamides.

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MATERIAL AND METHODS

The 32 volunteers employed in this investigation were obtained from the enlisted personnel of two newly formed General Hospitals stationed at an Army post. The men had passed the regular physical examination of the Army and had either been brought together when the hospitals had been activated, or assigned at a later date from a general pool. They were housed with the others of their respective complements and continued their regular duties and classes throughout the period of the study. With this background the men were extremely cooperative and fell readily into the spirit of the investigation.

Two groups of 16 men were formed and a definite schedule of observations arranged. Group A reported to the laboratory 1½ hours after breakfast on each Monday morning and the drugs were administered 1 hour thereafter. The blood samples were taken before and after ingestion of the drugs at regular pre-determined intervals. The men ate their lunch at 12 noon and dinner at 5:30 p. m. with their own organizations. Water was available but there was no access to refreshments such as coffee, soft drinks or food between meals. Between the evening blood samples at 7:00 to 7:30 p. m. and 11:00 to 11:30 p. m., the men were allowed to go to the movies or the post exchange where food and beverages could be purchased. Except for these periods, the men were under supervision in the field laboratory from 8:00 a. m. until 12 midnight. A day room and recreational facilities were provided during the time spent in the laboratory. They reported again on Tuesday morning for the 24-hour blood sample. Group B followed the same program, except that these men came in Thursday and Friday of each week.

In this manner, each group was followed for 24 hours and then released from observation for one week. All those receiving the 1 gram doses of the various sulfonamide compounds were studied on one day and those receiving 2 grams on another. A roster was kept and the men were taken in order, both for the administration of the drugs and the sampling of the blood, so that the desired spacing of time intervals was rigidly maintained.

The courses of drug were staggered to accommodate for variation in environmental conditions. Instead of employing a single drug each week, one compound was given to only four men so that all four of the selected sulfonamides were studied at the same time and dosage. For

example, on the first trial, the men numbered A_1 to A_4, inclusive, received 1 gram of sulfanilamide; A_5 to A_8, sulfadiazine; A_9 to A_{12}, sulfamerazine; and A_{13} to A_{16}, sulfamethazine. The following week, A_1 to A_4 received 1 gram of sulfamethazine; A_5 to A_8, sulfanilamide; A_9 to A_{12}, sulfadiazine; and A_{13} to A_{16}, sulfamerazine. A like alternation was employed for the men in Group B who received the 2-gram doses of the same compounds. With this program of weekly rotation, the individuals in Groups A and B received a single dose of either 1 or 2 grams of each of the four drugs. The decision to employ these quantities in the investigation was made because of the increasing use of doses of this size of the sulfonamides in the chemoprophylaxis of various bacterial infections.

The sulfonamide compounds were given in tablet form as prepared for general therapeutic use. Each tablet contained 0.5 grams (7.5 grains) of the drug. Thus, 2 tablets were required for the 1-gram and 4 for the 2-gram doses. They were taken by mouth and swallowed whole. The men were specifically instructed not to crush the tablet.

Finger blood samples for drug determination were drawn just before the drug was administered (0 hours), as well as 2, 4, 6, 10, 14, and 24 hours after ingestion. In some instances a 1-hour determination was made. The skin of the finger was cleansed with acetone which was allowed to evaporate completely. The antero-distal pad was then nicked, using a mechanical spring lancet, to permit a free flow of blood. The first drops were wiped away with a fresh absorbent tissue and then 0.1 ml. was drawn into a calibrated capillary pipette. The measured sample thus obtained was carefully expelled into the bottom of a shell vial containing 3.9 ml. of distilled water. The pipette was then repeatedly rinsed with the upper clear layer. The water and blood in this vial were well mixed. This 1:40 dilution was sufficient to hemolyze the red blood corpuscles. A separate pipette was employed for each individual. The pipettes were subsequently cleaned with chromic acid cleaning solution, rinsed with distilled water and acetone and dried before being used again.

The diluted and hemolyzed specimens of blood were stored in the refrigerator until the drug determinations could be performed. The procedure employed, suggested by Dr. E. K. Marshall, was a modifica-

tion of the micro-technique described by Marshall and Bratton.[6] The various steps are presented in detail.

To precipitate the proteins, trichloracetic acid (1.0 ml. of a 15 per cent solution) was carefully measured into each of the vials containing the 4.0 ml. of diluted and hemolyzed blood. The acidified mixture was thoroughly shaken for five minutes and then filtered through a Whatman #5 paper. Three ml. of the filtrate were transferred with a volumetric pipette to a calibrated colorimeter tube and 0.5 ml. of a 0.05 per cent solution of sodium nitrite added. The tubes were well shaken and the reaction was allowed to proceed for 3 minutes. At that time, 0.5 ml. of a 0.25 per cent solution of ammonium sulfamate (La Motte) was added and mixed with the contents of the tube. After an interval of 2 minutes, 1.0 ml. of a 0.025 per cent solution of N(1-naphthyl) ethelenediamine hydrochloride (La Motte) was added, the tubes shaken and placed in a covered rack for 10 minutes to allow color to develop. The intensity of this color was then determined by employing a Klett Summerson photoelectric colorimeter with the green filter #54.

The estimations of sulfonamide blood levels other than sulfanilamide were made with the same procedure and measured against the standard sulfanilamide solution. In these instances the final colorimetric readings were multiplied by the appropriate factors. These factors, obtained from comparative determinations made in the laboratory of Dr. E. K. Marshall, were: sulfadiazine, 1.43; sulfamerazine, 1.56; and sulfamethazine, 1.70. The estimations of drug concentrations in known sulfadiazine and sulfamerazine solutions prepared in the field laboratory, employing these factors, were in good agreement as illustrated by the results given in Table 1.

The reagents were of the highest quality. Duplicate runs were frequently made, employing the chemicals routinely used in this study and those furnished by Dr. Marshall. The solutions of sodium nitrite, ammonium sulfamate and ethelenediamine hydrochloride were prepared on the day that determinations were made. The trichloracetic acid solution was made each week. One liter of the standard sulfanilamide solution (10 mg. per cent) was prepared at the beginning of the study and used throughout. The 5 mg. per cent standard employed was freshly prepared from this stock solution each time. An aliquot of the 10 mg. per cent sulfanilamide standard was assayed during the course of the study in the laboratory of Dr. Marshall and was found to contain 9.92 mg. per 100 ml. All solutions were kept, when not required, in glass-stoppered bottles in a refrigerator held at 5°C.

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[6] Bratton, C. H. and Marshall, E. K. A new coupling component for sulfanilamide determination. *Jour. Biol. Chem.*, 1939, 125: 537.

TABLE 1

Recovery values from solutions containing 10 mg. per 100 ml. of sulfadiazine and sulfamerazine

DRUG	MENSTRUUM	CONCENTRATION DETERMINED*
Sulfadiazine	Distilled water	9.7-9.4-9.7-9.7
	Defibrinated blood	9.4-9.4
Sulfamerazine	Distilled water	9.6-9.6-9.6-10.0
	Defibrinated blood	10.0-9.4

* Concentration determined employing factors furnished by Dr. E. K. Marshall.

The two major errors encountered in the pilot titrations were (1) incomplete precipitation of the protein due to inadequate mixing (time and thoroughness) of the trichloracetic acid solution with the hemolyzed blood sample; and (2) incomplete neutralization of the sodium nitrite with the ammonium sulfamate resulting in a fine colloidal precipitation of the dye in a colorless form.

By following a constant and rigidly controlled procedure, as described, most of the technical errors were minimized and any significant deviation from the prescribed procedure could be detected readily by an unusual color reading of standard sulfanilamide solution, normal serum, or distilled water blanks. The delicacy and accuracy of the technique were well supported by the values obtained in the determinations made in the aforementioned manner on the standard sulfanilamide solution during the course of the investigation. The frequency distributions of the colorimetric readings, together with the means and their standard errors, are presented in Table 2.

All values for the sulfonamide concentrations were corrected for the trace of color contributed by the blood, by subtraction of the average of the colorimetric readings obtained with the pre-drug blood blanks each day. The testing of the blood of all subjects prior to the administration of the drug likewise permitted detection of any prior unsuspected absorption of drug. Although this problem did not arise with the men in the study groups, significant drug levels were found in specimens of blood taken from other individuals for control purposes. These men

TABLE 2

Colorimetric values on standard sulfanilamide solution at various times during study period

5 MG. PER CENT STANDARD		10 MG. PER CENT STANDARD	
Colorimetric reading	Frequency	Colorimetric reading	Frequency
90	1	190	0
91	0	191	0
92	4	192	1
93	5	193	3
94	7	194	5
95	11	195	3
96	8	196	0
97	10	197	1
98	18	198	3
99	14	199	0
100	12	200	0
101	3		
102	2		
103	1		
104	1		
105	0		
106	1		
107	1		
Total	99		16
Average reading	97.4 ± .3		194.8 ± .5

denied ingestion of drug but in the two instances enquiry revealed that sulfathiazole ointment had been applied once for a burn and once for a dermatitis.

The men were closely observed and questioned each week as to the occurrence of any symptoms that might be remotely related to the repeated ingestion of the various sulfonamides. Examination of the blood and urine were made four hours after a drug was administered. The hematological procedures consisted of determination of the hemoglobin level, red and white cell counts, and an examination of a stained

smear with the differential classification of at least 100 leukocytes. The urine was tested for the presence of albumin and the sediment was studied microscopically. These procedures were carried out by the technician of the station hospital laboratory routinely assigned to this type of work. No unusual responses were observed.

RESULTS

The observations on the individual drug levels attained following the administration of the various sulfonamides are presented in Tables 1 2, 3, and 4 of Appendix B. As there was no correlation between the blood levels attained and the body weight in these groups, it was considered unnecessary to make any adjustment for this factor.

Repeated ingestion of the sulfonamide compounds at weekly intervals did not influence the absorption and excretion, as determined by repeated blood levels. This is illustrated in the tabulation of the observed values as presented in Appendix B, Table 5.

The mean levels at successive time periods are shown in Table 3 of the text. In order to obtain meaningful constants summarizing the characteristics of each drug, a curve was derived and fitted for each of the drugs. It was from this equation that the theoretical mean levels included in Table 3 were calculated. The curve was derived on the following assumptions as to the underlying biological processes:

(1) After the oral administration of the drug, a certain amount of it eventually enters the blood stream, the rest being eliminated without prior absorption. There is a lag before the drug appears in the blood. Thereafter its absorption proceeds at an exponential rate, that is, a constant proportion of the amount remaining to be absorbed enters the blood stream per minute. The amount remaining to be absorbed at any time is the difference between that which will eventually pass into the blood stream and that which has already passed. The amount of drug secreted into the intestinal tract and also available for reabsorption is thus neglected.

(2) The free drug is removed from the blood stream by fecal and renal excretion and by acetylation. This combined elimination takes place at an exponential rate, that is, a constant proportion of the amount of free drug in the blood stream at any time is eliminated per minute.

(3) Throughout the process, there is a transcapillary exchange of the drug between the vascular and extravascular fluids, but this is at

TABLE 3

Observed and calculated mean levels of non-acetylated drug in milligrams per cent of whole blood at successive times after administration in a single dose of 1 gram and 2 grams of four sulfonamide compounds

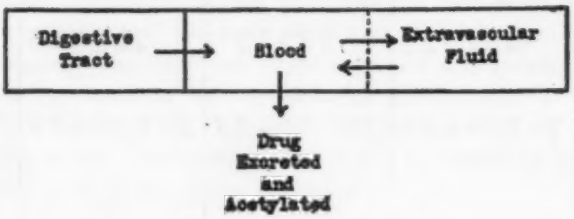
TABLE 3

Observed and calculated mean levels of non-acetylated drug in milligrams per cent of whole blood at successive times after administration in a single dose of 1 gram and 2 grams of four sulfonamide compounds

DRUG	1 GRAM SINGLE DOSE					2 GRAM SINGLE DOSE				
	Time in hours	Observed mean	Standard error	Calculated mean	Difference (observed-calculated)	Time in hours	Observed mean	Standard error	Calculated mean	Difference (observed-calculated)
Sulfanilamide	0.5			0.00		0.5			0.00	
	1	1.4	±0.36	1.40	0.00	1			2.66	
	2	2.0	±0.08	1.83	+0.17	2	3.7	±0.12	3.49	+0.21
	4	1.5	±0.06	1.62	−0.12	4	3.0	±0.16	3.09	−0.09
	6	1.4	±0.08	1.39	+0.01	6	2.5	±0.09	2.65	−0.15
	10	1.0	±0.06	1.02	−0.02	10	1.9	±0.07	1.94	−0.04
	14	0.7	±0.04	0.75	−0.05	14	1.5	±0.07	1.43	+0.07
	24	0.4	±0.03	0.35	+0.05	24	0.9	±0.06	0.66	+0.24
Sulfadiazine	0.5			0.00		0.5			0.00	
	1	0.4	±0.20	0.59	−0.19	1			0.94	
	2	1.1	±0.12	1.31	−0.21	2	2.3	±0.28	2.08	+0.22
	4	1.8	±0.10	1.79	+0.01	4	3.5	±0.44	2.84	+0.66
	6	1.7	±0.10	1.78	−0.08	6	2.8	±0.23	2.84	−0.04
	10	1.5	±0.10	1.49	−0.01	10	2.2	±0.21	2.37	−0.17
	14	1.2	±0.06	1.22	−0.02	14	1.8	±0.16	1.90	−0.10
	24	0.8	±0.04	0.68	+0.12	24	1.2	±0.16	1.07	+0.13
Sulfamerazine	0.5			0.00		0.5			0.00	
	1	2.2	±0.29	1.97	+0.23	1			2.94	
	2	3.5	±0.14	3.44	+0.06	2	4.4	±0.36	5.11	−0.71
	4	3.6	±0.16	3.67	−0.07	4	5.6	±0.36	5.44	+0.16
	6	3.4	±0.17	3.40	0.00	6	5.0	±0.31	5.06	−0.06
	10	3.0	±0.11	2.86	+0.14	10	4.1	±0.33	4.26	−0.16
	14	2.4	±0.17	2.41	−0.01	14	3.6	±0.32	3.59	+0.01
	24	1.8	±0.17	1.56	+0.24	24	2.6	±0.27	2.34	+0.26
Sulfamethazine	0.5			0.00		0.5			0.00	
	1	1.7	±0.59	1.93	−0.23	1			3.18	
	2	3.1	±0.24	2.73	+0.37	2	4.4	±0.37	4.50	−0.10
	4	2.2	±0.26	2.30	−0.10	4	3.8	±0.59	3.79	+0.01
	6	1.6	±0.25	1.80	−0.20	6	2.9	±0.48	2.96	−0.06
	10	1.1	±0.20	1.09	+0.01	10	1.8	±0.43	1.79	+0.01
	14	0.6	±0.10	0.66	−0.06	14	1.2	±0.35	1.09	+0.11
	24	0.1	±0.04	0.19	−0.09	24	0.5	±0.14	0.31	+0.19

such a rapid rate relative to the rates of absorption and elimination that these two fluid compartments[7] may be considered in dynamic equilibrium at all times. This implies that the amount eliminated from the system per minute is not only a constant proportion of the amount in the blood at any time, but also a constant (but different) proportion of the amount contained in the entire vascular and extravascular fluid systems.

Diagrammatically these assumptions may be represented in the following scheme:



The dotted line between the blood and extravascular fluid compartments signifies that these two are at all times in equilibrium. This does not mean that the concentration of drug in the two fluids is necessarily the same, but rather that there is a constant ratio of the drug concentrations in the two fluids. Each drug has a characteristic ratio of these concentrations.

These assumptions result in the following double exponential equation to describe the relationship between concentration, expressed as milligrams per 100 ml. of drug in the blood, y, and time in minutes after ingestion, t:

$$y = -Ke^{-b_1(t-t_c)} + Ke^{-b_2(t-t_c)} \qquad (1)$$

In this equation t_c is the time between ingestion and the first appearance of the drug in the blood; b_1 is the rate of absorption (proportion absorbed per minute of the amount remaining to be absorbed); b_2 is the rate of elimination (proportion eliminated per minute of that amount present in the entire vascular and extravascular fluid compartments); K is the constant of integration and is dependent upon the total amount

[7] The term "fluid compartment" refers to that volume accessible to the given drug.

of the drug absorbed, the volume of the fluid compartments and the rates of absorption and elimination of the drug.[8]

It will be noted that when $t = t_e$, $y = 0$, that is, the reaction starts at this time. At earlier times, y is negative and the equation does not apply over this interval.

The equation was fitted by a graphical procedure to the observed means, in order to derive the arithmetic values of the constants. It was found that a lag of approximately 30 minutes was present and there was no evidence that this value differed for the four drugs examined. Therefore, t_e, the interval between the oral administration of the drug and its first appearance in the blood stream, was taken as 30 minutes in every case. The equations derived for the different drugs at the indicated doses are as follows:

Sulfanilamide

1 gm. $y = -2.13\, e^{-.0395\,(t-30)} + 2.13\, e^{-.00128\,(t-30)}$

2 gm. $y = -4.05\, e^{-.0395\,(t-30)} + 4.05\, e^{-.00128\,(t-30)}$

Sulfadiazine

1 gm. $y = -2.57\, e^{-.00992\,(t-30)} + 2.57\, e^{-.000950\,(t-30)}$

2 gm. $y = -4.08\, e^{-.00992\,(t-30)} + 4.08\, e^{-.000950\,(t-30)}$

Sulfamerazine

1 gm. $y = -4.31\, e^{-.0218\,(t-30)} + 4.31\, e^{-.000717\,(t-30)}$

2 gm. $y = -6.41\, e^{-.0218\,(t-30)} + 6.41\, e^{-.000717\,(t-30)}$

Sulfamethazine

1 gm. $y = -3.57\, e^{-.0307\,(t-30)} + 3.57\, e^{-.00208\,(t-30)}$

2 gm. $y = -5.88\, e^{-.0307\,(t-30)} + 5.88\, e^{-.00208\,(t-30)}$

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[8] For a complete derivation of this equation and those that follow, see Appendix A.

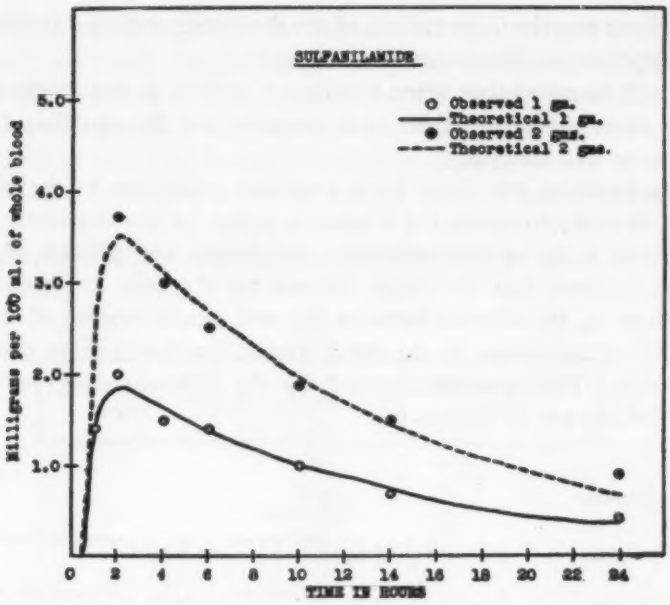

FIG. 1. MEAN BLOOD LEVELS OF DRUG AT SUCCESSIVE TIMES AFTER INGESTION OF A SINGLE DOSE

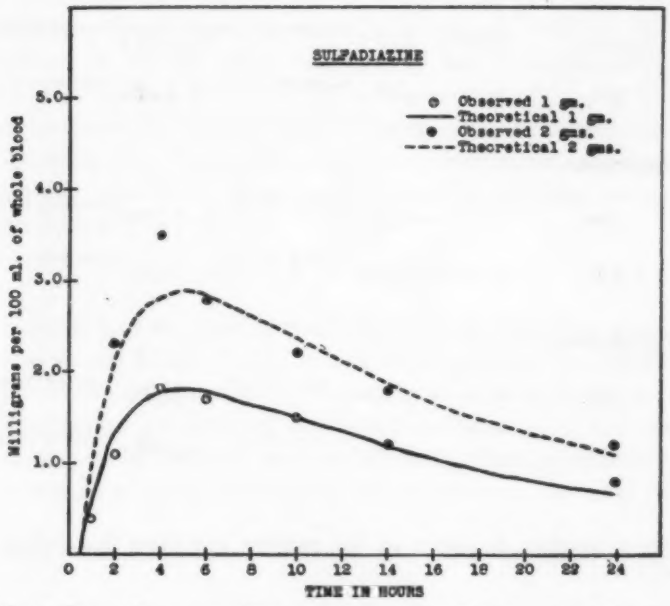

FIG. 2. MEAN BLOOD LEVELS OF DRUG AT SUCCESSIVE TIMES AFTER INGESTION OF A SINGLE DOSE

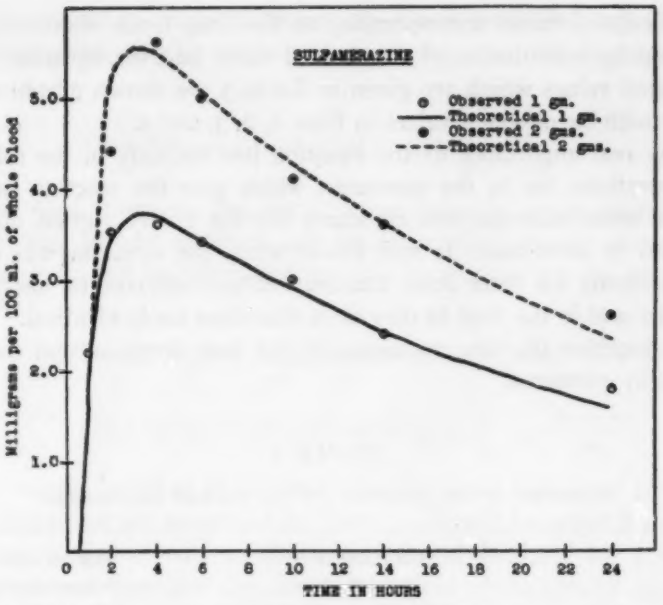

FIG. 3. MEAN BLOOD LEVELS OF DRUG AT SUCCESSIVE TIMES AFTER INGESTION OF A SINGLE DOSE

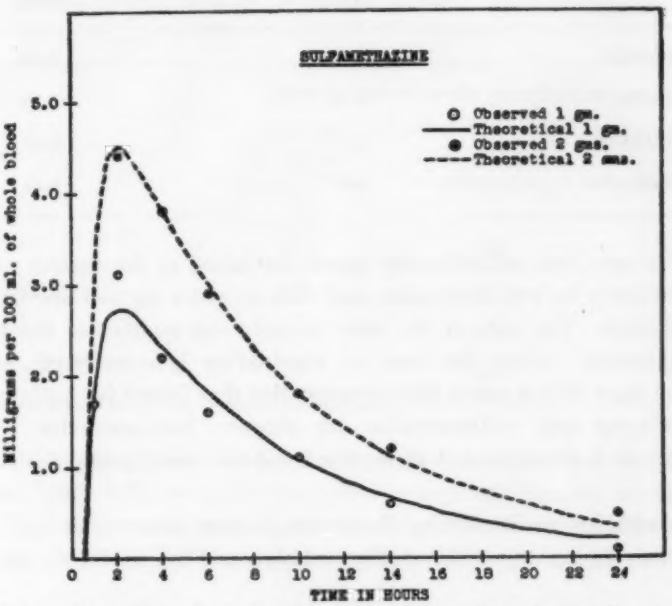

FIG. 4. MEAN BLOOD LEVELS OF DRUG AT SUCCESSIVE TIMES AFTER INGESTION OF A SINGLE DOSE

Calculated values corresponding to the drug levels observed can be obtained by substitution of the desired times into the equation. These calculated values which are given in Table 3 are shown graphically together with the observed values in Figs. 1, 2, 3, and 4.

The real importance of the equation lies not only in the calculated concentrations but in the constants, which give the reaction rates. It will be noted that the rate constants for the 1 and 2-gram doses are identical in each case. It was found when the equation was derived independently for these doses that the constants differed by insignificant amounts and in the final fit they were therefore made identical. Table 4 brings together the rate constants for the four drugs so that they may be readily compared.

TABLE 4

Constants of the equations for the various sulfonamides

DRUG	PERCENTAGE OF UNABSORBED NON-ACETYLATED DRUG ENTERING BLOOD PER MINUTE $100b_1$	PERCENTAGE OF NON-ACETYLATED DRUG IN BLOOD AND EXTRAVASCULAR FLUIDS ELIMINATED PER MINUTE $100b_2$
Sulfanilamide	3.95	0.13
Sulfadiazine	0.99	0.10
Sulfamerazine	2.18	0.07
Sulfamethazine	3.07	0.21

It is seen that sulfanilamide enters the blood at the fastest rate, followed closely by sulfamethazine and then in order by sulfamerazine and sulfadiazine. The rate of the latter is only one quarter of the rate for sulfanilamide. When the rate of elimination is considered, sulfamethazine leads with a rate a third greater than that found for sulfanilamide. Sulfadiazine and sulfamerazine are slower. Sulfamerazine with the lowest rate is eliminated at about one third the speed found for sulfamethazine.

In addition to furnishing direct comparison, these rates may be employed to derive other descriptive constants. One of these, the period

of time required to attain the maximum blood level after ingestion of the sulfonamides, may be obtained by employing the following equation:

$$\text{Time for maximum level} = t_c + \frac{\ln \frac{b_1}{b_2}}{b_1 - b_2} \qquad (2)$$

Two other constants, the period after ingestion when 50 per cent of each drug will be absorbed and similarly when 50 per cent of the absorbed drug will be eliminated may be determined by the following equations:

$$\text{Time for 50\% absorption} = t_c - \frac{\ln (.5)}{b_1} \qquad (3)$$

$$\text{Time for 50\% elimination} = t_c - \frac{1}{b_2} \ln \frac{b_1 - b_2}{2b_1} \qquad (4)$$

The values for these three constants have been calculated for each of the drugs and are presented in Table 5. It will be noted that these values are dependent only on constants that are the same for 1 and 2-gram doses, and therefore they are independent of the size of the dose.

TABLE 5

Period of time required for various stages in the absorption and excretion of the sulfonamides

DRUG	TIME IN HOURS AFTER INGESTION TO ATTAIN		
	Maximum concentration	50% absorption	50% elimination
Sulfanilamide	2.0	0.8	10.0
Sulfadiazine	4.9	1.7	14.4
Sulfamerazine	3.2	1.0	17.4
Sulfamethazine	2.1	0.9	6.6

Sulfanilamide and sulfamethazine required two hours to reach the maximum level, sulfamerazine three hours, and sulfadiazine about five hours. This time period is a function of both the rates of absorption and of elimination. The times for 50 per cent completion of reactions

are often used for comparative presentation because they are reliable and descriptive expressions of the speed of these reactions. With reference to the time for 50 per cent absorption, sulfanilamide, sulfamerazine, and sulfamethazine were similar while sulfadiazine was markedly prolonged. This time is a function of the absorption rate. A greater variation was noted in the time for elimination of these compounds, which might be expected since it depends on both absorption and elimination rates. Sulfamerazine was slowest, taking 17.4 hours for 50 per cent elimination as compared to the 6.6 hours required for sulfamethazine, the most rapid.

The maximum blood level may be calculated by substitution in the following equation derived from equation (1):

$$\text{Maximum blood level} = -K\left(\frac{b_1}{b_2}\right)^{-\frac{b_1}{b_1-b_2}} + K\left(\frac{b_1}{b_2}\right)^{-\frac{b_2}{b_1-b_2}} \qquad (5)$$

It is generally accepted that the activity of a drug is related not only to the level attained but also to the time interval that it is maintained. It is desirable, therefore, to select a single expression which will depict the combined effect of these two variables. The area under the curve, as a function of time and level (milligram-hours of non-acetylated drug), furnishes a satisfactory representation. It is determined through integration of the basic equation (1) for any time period desired.

The following equation pertains to the 24 hours following ingestion of the drug:

$$\text{Milligram-hours for the first 24 hours} = \frac{K\,(b_1 - b_2)}{b_1\,b_2} + \frac{K}{b_1}\,e^{-b_1(24-t_c)} - \frac{K}{b_2}\,e^{-b_2(24-t_c)} \qquad (6)$$

where t_c, b_1, and b_2 are expressed on a time scale of hours.

The values for the four drugs, determined from equations (5) and (6), are given in Table 6.

Sulfamerazine attained the highest level and the greatest area under the curve of any of the drugs. Sulfadiazine had the lowest maximum level but the milligram-hours for this drug exceeded those for sulfamethazine and sulfanilamide.

When the compounds were compared by calculation of the proportionate increases obtained by doubling the dosage, it was found that the maximal level of sulfanilamide was increased 94 per cent, sulfamethazine 67 per cent, sulfadiazine 59 per cent and sulfamerazine only

TABLE 6

Milligram-hours of non-acetylated drug and the maximal blood levels for the various sulfonamides

DRUG	DOSAGE (in grams)	MAXIMUM BLOOD LEVEL (in mg. per 100 ml.) y_{max}	MILLIGRAM-HOURS PER 100 ML. WHOLE BLOOD WITHIN 24 HOURS AFTER INGESTION
Sulfanilamide	1	1.8	22.2
	2	3.5	42.3
Sulfadiazine	1	1.8	28.9
	2	2.9	46.0
Sulfamerazine	1	3.7	60.4
	2	5.5	89.8
Sulfamethazine	1	2.7	25.1
	2	4.5	41.4

49 per cent. The same proportionate increases were noted when the area subtended by the curve was considered.

One further use that may be mentioned for the derived equation relates to critical blood level. Should a critical level, $y = q$, of a drug be required before its antibacterial activity becomes manifest, the times when this level will be attained, its duration, and milligram-hours of available drug above the level can be readily computed. If the necessary level to be surpassed is less than the maximum, then it will be observed twice, once as the amount of drug in the blood rises and again as it falls. Between these two times, the blood concentration will be above the critical level q. If these two times are t_a and t_b, respectively, the milligram-hours of non-acetylated drug per 100 ml. of whole blood above this level q can be computed by substitution in equation (7).

$$\text{Milligram-hours above level } q = \frac{K}{b_1} e^{b_1 t_c}\left[e^{-b_1 t_b} - e^{-b_1 t_a}\right] - \frac{K e^{b_2 t_c}}{b_2}\left[e^{-b_2 t_b} - e^{-b_2 t_a}\right] - q\,(t_b - t_a) \quad (7)$$

where b_1, b_2, and t_c are expressed on a time scale of hours.

Furthermore, when a program of chemoprophylaxis requiring repeated doses is planned, knowledge of the basic equation (1) and the inherent constants for the specific drug would be a distinct aid. The blood levels to be expected with a single dose or any other regime could be determined readily by a simple addition of the calculated values for the drug at the dosage and time intervals selected. This procedure requires the assumption that the additional concentration produced by any given dose is independent of that produced by previous doses. The additive equation employed is given in Appendix A. The application of this equation to three different schedules of sulfadiazine is illustrated in Table 7.

As indicated in Table 7, the difference in blood levels becomes stabilized at the various dosage schedules of sulfadiazine. When one or two grams are given daily, the levels attain a constant daily differential on the fourth day. A single preparatory dose of 2 grams followed by the daily administration of 1 gram prolongs this period only slightly. If the necessary blood levels can be estimated, the use of this equation will permit the selection of the proper schedule for a program of chemoprophylaxis.

SUMMARY AND CONCLUSION

The absorption, persistence and elimination of four sulfonamides, sulfanilamide, sulfadiazine, sulfamerazine and sulfamethazine, were compared by determining at stated intervals the concentration of the various compounds in the peripheral blood. The drugs were administered orally in one and two-gram doses to normal young soldiers under controlled conditions.

The results were summarized for comparative purposes by derivation of a double exponential equation. This equation was fitted by a graphical procedure to the observed means, in order to derive the arithmetic values of the constants. Substitution of these values permitted the calculation of expressions indicating the relationship of absorption, persistence and elimination of the four sulfonamides.

When these were employed in the comparison of the four drugs, it was found that although sulfanilamide had the fastest rate of absorption and sulfamethazine the highest maximum level, the largest number of milligram-hours of available drug was found after the ingestion of sulfamerazine because of its extremely low rate of elimination. Sulfa-

TABLE 7

Anticipated blood levels with various schedules of sulfadiazine

SCHEDULE OF ADMINISTRATION	TIME																	
	Day	1		2		3		4		5		6		7		8		
	Hour	4	24	28	48	52	72	76	96	100	120	124	144	148	168	172	192
1 gm. single dose		1.79	.68	.54	.17	.14	.05	.04	.01	.01	0	0	0	0	0	0	0
2 gm. single dose		2.84	1.07	.86	.28	.22	.07	.06	.02	.02	.01	0	0	0	0	0	0
1 gm. daily		1.79	.68	2.33	.85	2.47	.90	2.51	.91	2.52	.91	2.52	.91	2.52	.91	2.52	.91
2 gm. daily		2.84	1.07	3.70	1.35	3.92	1.42	3.98	1.44	4.00	1.45	4.00	1.45	4.00	1.45	4.00	1.45
2 gm. initial followed by 1 gm. daily		2.84	1.07	2.65	.96	2.55	.92	2.53	.92	2.53	.92	2.52	.92	2.52	.91	2.52	.91

diazine had the lowest rate of absorption and lowest maximum level and yet, due to the fact that the rate of elimination approached the value of sulfamerazine, the number of milligram-hours of available drug exceeded that of sulfanilamide and sulfamethazine.

Sulfamerazine would be the drug of choice for prophylaxis or therapy on the basis of these findings. However, other factors such as plasma binding and antibacterial activity of the various compounds play a role in the final decision. These will be evaluated in subsequent papers.

The derivation and possible applications of the equation to other problems are presented.

APPENDIX A

I. DERIVATION OF EQUATION (1) OF THE TEXT

a. Assumptions

If a single dose of a given sulfa drug is administered orally, the drug appears in the blood stream and exhibits changing blood levels with time. An equation showing the relationship of free (non-acetylated) drug concentration in the blood, and time elapsed after administration, is derived under the following assumptions:

(i) After the oral administration of the drug, there is a lag before the appearance of the drug in the blood but after this time the absorption proceeds at an exponential rate, that is, a constant proportion of the amount remaining to be absorbed is absorbed per unit of time. The amount remaining to be absorbed at any time is the difference between the amount which eventually passes into the blood stream and that which has already passed into the blood stream. The amount of drug secreted into the intestinal tract and available for reabsorption is thus neglected.

(ii) The free drug is eliminated from the blood stream by fecal and renal excretion and by acetylation, and this elimination takes place at an exponential rate, that is, a constant proportion of the amount of free drug in the blood stream at any time is eliminated per time unit.

(iii) Throughout the process, there is a transcapillary exchange of the drug between the vascular and extravascular fluids, but this is at such a rapid rate relative to the rates of absorption and elimination that the two fluid compartments may be considered in dynamic equilibrium at all times. This means that the amount eliminated from the system per time unit is not only a constant proportion of the amount in the blood at any time, but also a constant (but different) proportion of the amount in the entire vascular and extravascular systems.

b. Notation

t = time after administration of drug

t_c = time between administration of drug and first appearance in the blood stream

$t' = t - t_c$ = time after first appearance of drug in blood stream
A = amount of free drug eventually appearing in the blood
X = amount remaining to be absorbed at time t
Y = amount in blood at time t
CY = amount in combined vascular and extravascular fluids at time t
Z = amount eliminated from the vascular and extravascular fluids by time t
V_B = blood volume
V_B = extravascular fluid volume
$y = Y / V_B$ = concentration in the blood at time t
b_1 = proportion of X passing into blood per unit of time, at any instant
b_2 = proportion of CY eliminated per unit of time, at any instant.

c. Solution

Under assumption (i) the amount of drug remaining to be absorbed at time t' is given by

$$X = Ae^{-b_1 t'} \tag{1}$$

or the amount which has been absorbed into the blood stream up to any time t' is given by

$$A - X = A - Ae^{-b_1 t'} \tag{2}$$

Under assumption (iii) the vascular and extravascular concentrations may be considered in equilibrium at all times and therefore the total amount of drug in the two compartments combined is a constant, C, times the amount in the blood.* From assumptions (ii) and (iii), that a constant proportion of the total amount in these systems is eliminated per minute, we have that the amount eliminated by time t' is

$$Z = \int_0^{t'} b_2 (CY)\, dt' \tag{3}$$

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* The ratio of blood concentration to extravascular fluid concentration is given by $\frac{V_B}{V_B (C - 1)}$.

Then the amount present in the combined vascular and extravascular compartments at any time is given by the difference of the total amount absorbed and the total amount eliminated, up to that time, or

$$CY = A - Ae^{-b_1 t'} - \int_0^{t'} b_2 (CY)\, dt' \tag{4}$$

Differentiating (4) with regard to time, we have

$$\frac{dCY}{dt'} = Ab_1 e^{-b_1 t'} - b_2 CY \tag{5}$$

Dividing equation (5) by CV_B to get rate of change of concentration in the blood and substituting y for Y / V_B gives

$$\frac{dy}{dt'} + b_2 y = \frac{Ab_1}{CV_B} e^{-b_1 t'} \tag{6}$$

Equation (6) is a standard form of differential equation (see, for example, Murray, *Differential Equations*, 1921, p. 26) and has for its solution

$$y = \frac{-Ab_1}{CV_B (b_1 - b_2)} e^{-b_1 t'} + Ke^{-b_2 t'} \tag{7}$$

where K is the constant of integration.

Evaluating K under the condition that when $t' = 0$, $y = 0$, gives

$$y = -\frac{Ab_1}{CV_B (b_1 - b_2)} e^{-b_1 t'} + \frac{Ab_1}{CV_B (b_1 - b_2)} e^{-b_2 t'} \tag{8}$$

or in the form of equation (1) of the text

$$y = -Ke^{-b_1 (t - t_e)} + Ke^{-b_2 (t - t_e)} \tag{9}$$

II. TIME AND LEVEL OF MAXIMUM CONCENTRATION

Differentiating equation (9) with regard to time gives

$$\frac{dy}{dt} = b_1 Ke^{-b_1 (t - t_e)} - b_2 Ke^{-b_2 (t - t_e)} \tag{10}$$

Setting the derivative equal to 0, to determine the time of maximum concentration gives

$$b_1 e^{-b_1 (t - t_e)} = b_2 e^{-b_2 (t - t_e)} \tag{11}$$

Taking logarithms to the base e, we have

$$\ln b_1 - b_1 (t - t_c) = \ln b_2 - b_2 (t - t_c) \tag{12}$$

or

$$t - t_c = \frac{\ln \frac{b_1}{b_2}}{b_1 - b_2} \tag{13}$$

gives the time of maximum concentration. Substituting this value of $t - t_c$ in equation (9), we have

$$y_{max} = -Ke^{-\frac{b_1}{b_1 - b_2} \ln \frac{b_1}{b_2}} + Ke^{-\frac{b_2}{b_1 - b_2} \ln \frac{b_1}{b_2}} \tag{14}$$

Since the exponents are equivalent to

$$\ln \left(\frac{b_1}{b_2}\right)^{-\frac{b_1}{b_1 - b_2}} \text{ and } \ln \left(\frac{b_1}{b_2}\right)^{-\frac{b_2}{b_1 - b_2}}, \text{ respectively,}$$

and since by definition of logarithms, $e^{\ln x} = x$, equation (14) may be written

$$y_{max} = -K \left(\frac{b_1}{b_2}\right)^{-\frac{b_1}{b_1 - b_2}} + K \left(\frac{b_1}{b_2}\right)^{-\frac{b_2}{b_1 - b_2}} \tag{15}$$

III. TIME AND LEVEL WHEN ABSORPTION IS 50 PER CENT COMPLETE

The time when the absorption is half completed is given by letting $X = .5A$ in equation (1). This gives

$$e^{-b_1 (t - t_c)} = 0.5 \tag{16}$$

or

$$t - t_c = -\frac{\ln 0.5}{b_1} \tag{17}$$

The blood level at this time is given by

$$y_{\frac{1}{2} abs.} = -Ke^{\ln 0.5} + Ke^{\frac{b_2}{b_1} \ln 0.5} \tag{18}$$

or, rearranging,

$$y_{\frac{1}{2}\,obs.} = -0.5K + K(0.5)^{\frac{b_2}{b_1}} \qquad (19)$$

IV. TIME AND LEVEL WHEN ELIMINATION IS 50 PER CENT COMPLETE

The equation for the amount, Z, eliminated up to any time can be obtained either from equation (3) or by subtracting from A the amount remaining to be absorbed (X) and the amount in the blood and extravascular systems (CY). This gives

$$Z = A + \frac{Ab_2}{b_1 - b_2} e^{-b_1(t-t_o)} - \frac{Ab_1}{b_1 - b_2} e^{-b_2(t-t_o)} \qquad (20)$$

Elimination will be half completed when $Z = 0.5A$. Substituting this value in equation (20) and dividing the equation by A results in the following expression

$$0.5 = -\frac{b_2}{b_1 - b_2} e^{-b_1(t-t_o)} + \frac{b_1}{b_1 - b_2} e^{-b_2(t-t_o)} \qquad (21)$$

This equation cannot be solved directly for t, but with the size of rates involved in the present problem, the first term in this equation becomes negligible for moderately large values of t, and an approximate solution is therefore obtained from

$$0.5 = \frac{b_1}{b_1 - b_2} e^{-b_2(t-t_o)} \qquad (22)$$

which gives

$$t - t_o = -\frac{1}{b_2} \ln \frac{b_1 - b_2}{2b_1} \qquad (23)$$

If a more exact solution of equation (21) is desired, Newton's method of approximation can be used with equation (23) furnishing the first approximation. The blood level at this time is given by substitution in equation (9).

$$y_{\frac{1}{2}elim.} = -K\left(\frac{b_1 - b_2}{2b_1}\right)^{\frac{b_1}{b_2}} + K\left(\frac{b_1 - b_2}{2b_1}\right) \qquad (24)$$

V. AREA UNDER THE CURVE (MILLIGRAM-HOURS PER 100 ML. BLOOD)

The total area is given by integrating equation (9) from $t = t_o$ to $t = \infty$,

$$\int_{t_c}^{\infty} y\,dt = \frac{K}{b_1} e^{-b_1(t-t_c)}\Big]_{t_c}^{\infty} - \frac{K}{b_2} e^{-b_2(t-t_c)}\Big]_{t_c}^{\infty}$$

$$= -\frac{K}{b_1} + \frac{K}{b_2} = \frac{K(b_1 - b_2)}{b_1 b_2} \qquad (25)$$

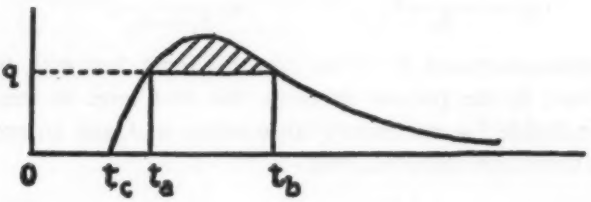
where b_1, b_2, and t are expressed on a time scale of hours.

For the first 24 hours after administration of the drug, the number of milligram-hours per 100 ml. blood is

$$\int_{t_c}^{24} y\,dt = \frac{K(b_1 - b_2)}{b_1 b_2} + \frac{K}{b_1} e^{-b_1(24-t_c)} - \frac{K}{b_2} e^{-b_2(24-t_c)} \qquad (26)$$

where t_c, b_1 and b_2 are expressed on a time scale of hours.

VI. CRITICAL LEVEL AND MILLIGRAM-HOURS PER 100 ML. ABOVE THIS LEVEL



Let q be a critical level of concentration achieved at time t_a, and again at time t_b, so that the blood level is above the critical level from time t_a to time t_b. The values of t_a and t_b at which y achieves the critical level can be obtained by methods of approximation, such as a graphical estimation. These values can then be refined, if necessary, by Newton's approximation.

With these values obtained, the number of milligram-hours per 100 ml. above this level is given by

$$\int_{t_a}^{t_b} y\,dt - q\,(t_b - t_a) = \frac{K}{b_1}\left[e^{-b_1(t_b-t_c)} - e^{-b_1(t_a-t_c)}\right]$$

$$- \frac{K}{b_2}\left[e^{-b_2(t_b-t_c)} - e^{-b_2(t_a-t_c)}\right] - q(t_b - t_a)$$

and factoring out $e^{b_1 t_c}$ and $e^{b_2 t_c}$,

$$\text{the area} = \frac{K}{b_1} e^{b_1 t_a} \left[e^{-b_1 t_b} - e^{-b_1 t_a} \right] - \frac{K e^{b_2 t_a}}{b_2} \left[e^{-b_2 t_b} - e^{-b_2 t_a} \right] - q(t_b - t_a) \tag{27}$$

VII. LEVEL RESULTING FROM REPEATED DOSES

Suppose that at n successive intervals of t_m, the dose is repeated. What is the level at any time t subsequent to the administration of the n-th dose, t being measured from the time of administration of the first dose?

Under the assumption that the additional level produced by any given dose is independent of that produced by previous doses, we would have a simple additive effect and thus

$$\begin{aligned} y = &- Ke^{-b_1(t-t_a)} + Ke^{-b_2(t-t_a)} - Ke^{-b_1(t-t_m-t_a)} + Ke^{-b_2(t-t_m-t_a)} \\ &- Ke^{-b_1(t-2t_m-t_a)} + Ke^{-b_2(t-2t_m-t_a)} \cdots \cdots \\ = &- K \sum_{\alpha=0}^{n} e^{-b_1(t-\alpha t_m-t_a)} + K \sum_{\alpha=0}^{n} e^{-b_2(t-\alpha t_m-t_a)} \end{aligned} \tag{28}$$

APPENDIX B

APPENDIX B, TABLE 1

APPENDIX B, TABLE 1

Observed levels of non-acetylated drug in milligram per cent of whole blood at successive times after administration in a single dose of 1 gram and 2 grams of ***sulfanilamide***

1 GRAM

TIME IN HOURS	Individuals																Observed mean	Standard deviation $\sqrt{\frac{\Sigma D^2}{n-1}}$	Standard error of observed mean $\frac{\sigma}{\sqrt{n}}$
	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	A_9	A_{10}	A_{11}	A_{12}	A_{13}	A_{14}	A_{15}	A_{17}			
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—
.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	—	—	—	—	1.2	0.5	2.2	1.6	1.4	.72	.357
2	1.8	2.4	2.4	1.9	1.9	1.9	1.8	2.3	2.3	2.3	1.7	2.4	1.6	1.4	2.2	1.9	2.0	.31	.080
4	1.4	1.4	1.2	1.4	1.4	1.6	1.6	1.7	1.5	2.0	2.0	1.5	1.3	1.3	1.4	1.3	1.5	.23	.059
6	1.4	1.3	1.0	1.3	1.5	1.3	1.3	1.6	1.5	1.3	2.0	1.5	1.2	0.7	1.2	1.0	1.4	.20	.075
10	1.0	1.0	0.9	1.1	1.1	1.1	0.9	1.2	1.3	1.3	1.4	1.2	0.8	0.5	—	0.9	1.0	.23	.061
14	0.6	0.6	0.7	0.7	0.6	0.7	0.8	0.8	0.9	0.6	0.8	1.0	0.4	0.4	0.6	0.8	0.7	.16	.041
24	0.3	0.2	0.4	0.4	0.4	0.4	0.7	0.5	0.5	0.6	0.4	0.6	0.3	0.3	0.5	0.4	0.4	.11	.028

2 GRAMS

	B_1	B_2	B_3	B_4	B_5	B_6	B_7	B_8	B_9	B_{10}	B_{11}	B_{12}	B_{13}	B_{14}	B_{15}	B_{16}			
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—
.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2	3.8	3.4	3.6	3.9	3.9	3.7	3.1	3.3	4.7	2.9	3.1	4.2	3.1	4.1	3.8	4.2	3.7	.48	.12
4	2.8	2.6	2.6	3.1	2.9	3.2	3.0	2.1	3.2	2.8	2.5	3.1	2.6	4.5	3.5	4.2	3.0	.60	.16
6	2.5	2.2	2.3	2.7	2.3	2.4	2.4	2.1	2.5	2.2	2.3	2.4	1.9	2.8	2.8	3.4	2.5	.33	.085
10	1.8	1.7	1.7	1.6	2.4	2.1	1.6	1.6	2.0	1.7	1.9	2.1	1.8	2.0	1.9	2.4	1.9	.25	.065
14	1.5	1.1	1.3	1.4	—	—	—	—	1.5	2.0	1.9	1.6	1.3	1.6	1.6	1.6	1.5	.25	.072
24	0.8	0.8	0.9	1.0	0.9	0.9	0.7	0.6	0.9	0.9	1.5	0.8	—	0.8	0.8	1.3	0.9	.22	.059

APPENDIX B, TABLE 2

Observed levels of non-acetylated drug in milligram per cent of whole blood at successive times after administration in a single dose of 1 gram and 2 grams of ***sulfadiazine***

1 GRAM

TIME IN HOURS	Individuals																Observed mean	Standard deviation $\sqrt{\frac{\Sigma D^2}{n-1}}$	Standard error of observed mean $\frac{\sigma}{\sqrt{n}}$
	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	A_9	A_{10}	A_{11}	A_{12}	A_{13}	A_{14}	A_{15}	A_{17}			
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—
.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	0	0.7	0.7	0	—	—	—	—	—	—	—	—	—	—	—	—	0.4	.40	.20
2	0.4	0.8	0.7	1.5	0.7	1.2	2.0	1.3	1.9	1.2	1.7	1.0	0.9	0.5	1.4	0.7	1.1	.47	.12
4	1.8	1.7	1.7	2.1	1.4	1.4	2.5	2.1	2.7	1.6	1.9	1.9	1.9	1.2	2.1	1.5	1.8	.39	.10
6	0.9	1.4	1.7	1.9	1.0	1.4	2.3	1.8	2.4	1.6	1.7	2.2	1.7	1.7	1.9	2.0	1.7	.40	.10
10	0.5	1.3	1.0	1.1	1.1	1.2	2.0	1.8	1.7	1.4	1.6	1.9	1.9	1.3	1.5	2.0	1.5	.39	.10
14	1.1	1.2	1.1	1.4	1.0	0.7	0.9	1.0	1.5	1.4	1.2	1.4	1.5	0.9	1.3	1.0	1.2	.23	.06
24	0.8	0.9	0.5	0.6	0.7	0.7	1.0	0.8	0.9	1.0	0.9	0.9	0.8	0.5	0.6	0.6	0.8	.16	.04

2 GRAMS

	B_1	B_2	B_3	B_4	B_5	B_6	B_7	B_8	B_9	B_{10}	B_{11}	B_{12}	B_{13}	B_{14}	B_{15}	B_{16}			
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—
.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2	4.1	3.9	2.4	3.9	1.1	1.4	2.3	1.2	3.8	1.7	1.2	1.9	1.4	3.2	2.2	1.4	2.3	1.1	.28
4	4.9	8.5	3.6	6.3	1.8	2.2	2.6	3.2	5.0	2.3	2.2	2.7	2.2	3.5	1.9	2.3	3.5	1.7	.44
6	4.4	4.3	2.3	4.7	2.2	1.9	2.0	3.0	4.3	1.9	1.9	2.5	1.9	3.2	2.0	2.8	2.8	0.9	.23
10	3.3	3.8	1.8	3.2	1.7	1.7	1.2	2.4	3.1	1.9	1.2	2.3	1.2	—	1.5	2.3	2.2	0.8	.21
14	2.9	2.3	1.3	2.0	1.4	1.4	1.1	2.1	—	—	—	—	1.2	—	1.7	2.2	1.8	0.5	.16
24	1.5	2.2	0.6	1.3	1.2	1.0	0.6	1.7	1.6	1.4	1.0	0.8	0.4	0.5	1.6	2.2	1.2	0.6	.16

APPENDIX B, TABLE 3

Observed levels of non-acetylated drug in milligram per cent of whole blood at successive times after administration

24	1.5	2.2	0.6	1.3	1.2	1.0	0.6	1.7	1.6	1.4	1.0	0.8	0.4	0.5	1.6	2.2	1.2	0.6	.16

APPENDIX B, TABLE 3

Observed levels of non-acetylated drug in milligram per cent of whole blood at successive times after administration in a single dose of 1 gram and 2 grams of ***sulfamerazine***

1 GRAM

TIME IN HOURS	Individuals																Observed mean	Standard deviation $\sqrt{\frac{\Sigma D^2}{n-1}}$	Standard error of observed mean $\frac{\sigma}{\sqrt{n}}$
	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	A_9	A_{10}	A_{11}	A_{12}	A_{13}	A_{14}	A_{15}	A_{17}			
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—
.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	2.1	1.5	2.2	2.9	—	—	—	—	—	—	—	—	2.2	.57	.29
2	1.8	3.4	3.5	3.8	3.6	2.8	3.7	4.1	4.3	4.3	3.0	3.8	4.1	—	3.6	2.8	3.5	.54	.14
4	3.2	3.2	3.7	4.0	3.7	3.3	3.0	3.7	3.4	3.5	5.6	3.8	3.3	—	3.4	3.6	3.6	.59	.16
6	3.2	3.2	4.4	4.0	3.4	3.2	3.0	3.1	3.0	3.0	5.0	2.6	2.7	—	3.3	3.3	3.4	.63	.17
10	3.0	3.0	3.0	3.6	2.8	2.9	2.7	3.1	2.0	2.6	3.8	3.0	2.5	—	3.0	3.3	3.0	.42	.11
14	1.7	2.2	2.5	2.9	3.2	3.1	2.7	2.1	1.8	1.4	3.5	1.8	1.6	—	2.7	3.1	2.4	.65	.17
24	—	2.2	1.6	2.5	1.5	2.5	1.1	1.1	0.9	1.5	2.5	1.9	1.0	—	2.3	2.5	1.8	.60	.17

2 GRAMS

	B_1	B_2	B_3	B_4	B_5	B_6	B_7	B_8	B_9	B_{10}	B_{11}	B_{12}	B_{13}	B_{14}	B_{15}	B_{16}			
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—
.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2	6.1	6.2	2.3	3.5	5.8	2.1	3.6	4.4	6.9	5.1	3.8	5.6	2.8	4.9	3.4	4.0	4.4	1.4	.36
4	6.6	7.0	3.2	5.0	7.0	3.6	4.9	4.6	7.6	8.6	5.6	5.6	4.1	5.2	5.2	5.2	5.6	1.4	.36
6	6.3	6.6	3.2	4.5	5.6	3.4	3.9	4.4	6.6	6.6	5.9	4.2	3.5	4.6	4.7	5.4	5.0	1.2	.31
10	6.1	6.2	2.8	3.6	4.6	2.3	2.6	4.3	5.2	—	5.1	3.7	2.8	3.5	—	4.5	4.1	1.2	.33
14	—	5.4	3.0	2.8	4.2	2.5	2.3	3.4	4.1	—	4.7	3.1	—	—	—	—	3.6	1.0	.32
24	4.1	3.8	2.7	1.8	3.0	1.8	1.3	3.0	2.8	—	3.6	2.0	1.4	1.1	2.8	3.9	2.6	1.0	.27

APPENDIX B, TABLE 4

Observed levels of non-acetylated drug in milligram per cent of whole blood at successive times after administration in a single dose of 1 gram and 2 grams of **sulfamethazine**

1 GRAM

TIME IN HOURS	Individuals																Observed mean	Standard deviation $\sqrt{\frac{\Sigma D^2}{n-1}}$	Standard error of observed mean $\frac{\sigma}{\sqrt{n}}$
	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	A_9	A_{10}	A_{11}	A_{12}	A_{13}	A_{14}	A_{15}	A_{17}			
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—
.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	0.5	1.9	3.2	1.0	—	—	—	—	1.7	1.18	.59
2	2.6	3.3	2.8	3.9	3.7	3.8	3.1	3.9	1.5	2.6	4.2	1.2	2.4	2.4	4.4	3.9	3.1	0.91	.24
4	1.0	2.7	2.6	3.3	2.6	2.4	1.5	1.6	1.0	0.9	4.3	2.7	0.8	1.3	3.5	3.5	2.2	1.00	.26
6	0.3	2.4	2.0	2.6	2.6	2.0	0.8	0.8	0.6	0.1	2.7	2.0	0.6	0.4	2.8	2.5	1.6	0.98	.25
10	0.0	1.9	1.3	1.9	2.1	1.6	0.8	0.5	0.1	0.0	2.2	1.4	0.2	0.2	1.6	1.7	1.1	0.76	.20
14	0.0	1.4	1.0	1.1	0.7	0.6	0.1	0.0	0.0	0.0	1.4	0.8	0.0	0.0	1.0	1.0	0.6	0.37	.096
24	0.0	0.0	0.3	0.3	0.2	0.4	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.4	0.4	0.1	0.15	.039

2 GRAMS

	B_1	B_2	B_3	B_4	B_5	B_6	B_7	B_8	B_9	B_{10}	B_{11}	B_{12}	B_{13}	B_{14}	B_{15}	B_{16}			
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—	—
.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2	6.1	5.5	3.2	4.3	4.9	3.9	3.5	5.9	1.0	6.0	3.4	5.7	2.7	—	3.4	6.6	4.4	1.4	.37
4	6.1	6.5	2.7	1.9	4.0	1.2	1.1	4.2	3.1	8.2	4.8	2.5	0.9	—	3.4	7.0	3.8	2.2	.59
6	5.6	5.0	1.2	0.6	2.6	1.0	0.9	3.9	4.2	5.9	4.0	1.9	0.2	—	2.0	4.8	2.9	1.8	.48
10	4.7	3.9	0.7	0.4	0.9	0.0	0.1	2.6	1.2	4.7	3.5	0.5	0.0	—	1.1	3.4	1.8	1.6	.43
14	—	—	—	—	0.8	0.3	0.3	1.6	0.5	3.6	2.9	0.0	0.0	—	0.4	2.5	1.2	1.1	.35
24	1.8	1.1	—	0.0	0.0	0.0	0.0	0.6	0.1	1.6	0.2	0.0	0.0	—	0.1	1.1	0.5	0.5	.14

24	1.8	1.1	—	0.0	0.0	0.0	0.0	0.6	0.1	1.6	0.2	0.0	0.0	—	0.1	1.1	0.5	0.5	.14

APPENDIX B, TABLE 5

The results of repetitive administration of sulfonamide drugs expressed as the average per man of the sum of the observed levels

ORDER IN WHICH SPECIFIED DRUG WAS GIVEN	ONE GRAM DOSE OF SPECIFIED SULFONAMIDE				TWO GRAM DOSE OF SPECIFIED SULFONAMIDE			
	Sulfanilamide	Sulfadiazine	Sulfamerazine	Sulfamethazine	Sulfanilamide	Sulfadiazine	Sulfamerazine	Sulfamethazine
1st	6.6	8.0	18.0	8.7	12.8	10.6	26.5	13.1
2nd	7.2	9.4	17.4	9.6	11.4	11.4	19.3	15.7
3rd	8.1	7.9	17.3	8.9	13.7	10.8	25.7	11.1
4th	5.6	7.0	17.3	7.5	15.8	19.9	22.1	17.4
Total for group	6.9	8.1	17.5	8.7	13.4	13.2	23.4	14.3

GROWTH CURVES OF NATIONS

BY J. D. KELLER

READERS of this journal are unquestionably familiar with growth curves of plants, animals and bacterial colonies—the well-known sigmoid or S-shaped curves[1]—but it is not so well known that the same general kind of curve applies also to other kinds of growth, such as that of a business enterprise, or of track mileage during the period of railway expansion.[2] So far as the author is aware, no studies have hitherto been made of the growth curves of nations or empires, and the object of the present paper is to set forth some tentative results of such a study of two cases.

When investigating the growth of a nation, what magnitude should be considered the measure of growth is a debatable question. It cannot be merely population, or territorial area, or numerical strength of army, or total wealth, or national income. It comprises all these and much more, especially the intangible or imponderable factors which in the case of an individual "count not as his worth yet swell the man's amount." Even the name to be used for the composite factor which is to form the ordinate of the growth curve, is debatable. "Valence" would probably suit, had it not a specialized meaning in chemistry. "Power" in the general rather than the engineering sense may serve fairly well, and is the term adopted here.

The first case considered will be that of Ancient Rome, the data for which, so far as available, are presented graphically in Fig. 1. The data for state income and for size of army were obtained from *An Economic Survey of Ancient Rome*,[3] the figures for population from the same work and from Mommsen.[4] The data for area of territory

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[1] d'Arcy W. Thompson, *On Growth and Form*, New York (Macmillan), 1942.

[2] A. J. Lotka, *Elements of Physical Biology*, Baltimore (Williams & Wilkins), 1925, page 369, Fig. 71.

[3] *An Economic Survey of Ancient Rome*, edited by Tenney Frank. 5 vols. Baltimore (Johns Hopkins Press), 1933-40.

[4] Th. Mommsen, *History of Rome*.

were calculated in the following way: the dates of acquisition of the various portions of territory are known, and approximately the limits of the modern countries or portions of countries to which the ancient designations correspond. The areas of the modern countries are accurately known, and are tabulated in the various atlases. By estimating the fraction of each modern country corresponding to each Roman conquest at a given period, the increments of Roman territory were obtained, and are tabulated in Table 1. There is of course some uncertainty in the exact square-mileage, but in percentage the error by this method should be satisfactorily low.

The territorial-area curve can thus be derived with sufficient accuracy, but this is the only one of the curves in Fig. 1 for which this

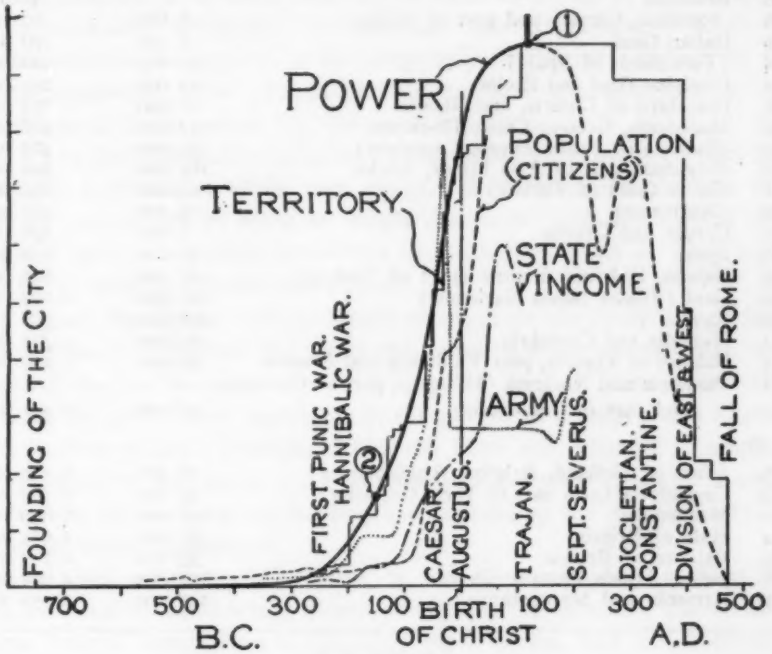

FIG. 1. GROWTH OF ANCIENT ROME

Scale of ordinates: Territory, 1 space = 200,000 square miles or 206,000,000 *jugera*
Population, 1 space = 1,000,000 citizens
State income (annual), 1 space = $10,000,000 or 50,000,000 *denarii*
Army, 1 space = 100,000 men

TABLE 1

Roman territorial increments and losses

YEAR	ANCIENT NAME (corresponding to modern territorial name)	AREA ADDED (OR LOST) (square miles)	TOTAL ROMAN AREA (square miles)
	Territory added		
B. C.			
540			600
440			600
338	Latium		2 400
290	Central Italy		17 000
273	Etruria and Southern Italy		40 000
268	Bruttium		42 800
238	(Sardinia, Corsica and part of Sicily)	18 660	61 460
220	Italian Gaul	8 540	70 000
194	(Two-thirds of Spain)	150 600	220 600
191	Cisalpine Gaul and Etolia	23 000	243 600
165	One-third of Liguria, and Rhodes	10 900	254 500
146	Macedonia, Greece, Crete, Illyricum	73 500	328 000
133	(Balance of Spain, except Cantabria)	35 000	363 000
129	Pergamus, part of Asia Minor, Africa	165 000	528 000
117	Cilicia (part of Turkey)	24 000	552 000
102	(Narbonne)	15 000	567 000
97	Cyrene and Cyprus	3 600	570 600
63	Syria	60 000	630 600
63	Galatia, Bithynia, Pontus (part of Turkey)	216 000	846 600
49	Gaul (France minus Narbonne)	196 200	1 042 800
30	Egypt	266 000	1 308 800
24	Numidia and Cantabria	65 000	1 373 800
14	Balance of Liguria, plus Vindelicia and Rhaetia	36 000	1 409 800
11	Pannonia and Noricum (Hungary, part of Germany and part of Jugoslavia)	98 000	1 507 800
A. D.			
9	(Part of Holland, Belgium, Luxembourg)	16 400	1 524 200
12	Cappadocia (also part of West Germany)	25 000	1 549 200
40	Mauretania	100 000	1 649 200
54	Half of Britain	33 000	1 682 200
84	Balance of Britain	33 000	1 715 200
106	Judea, Arabia Petraea, Dacia	191 000	1 906 200
117	Armenia and Mesopotamia	145 000	2 051 200
	Territory lost		
A. D.			
120	Armenia, Mesopotamia, North Britain		1 898 000
270	Dacia	116 000	1 782 000
395	(Eastern part of Empire lost by division)		976 200
410	Kingdom of the Vandals	268 200	708 000
415	Spain and Southern France		436 000
446	Britain		376 000
476	Fall of Rome		

can be said. As to population, the Roman census figures during the Republic and up to almost the zenith of the Empire, have survived, and are given by Mommsen; those for later periods seem to have perished. But even those available are of little value, for the following reasons. Up to almost the end of the Republic, the Roman census showed the number of adult male citizens of the city of Rome only, plus a few colonies or plantations. It excluded not only women, children and slaves, but also the bulk of the adult male inhabitants of the associated and conquered territories, even the citizens of the Latin Confederation. The first large extension of citizenship to other than native Romans occurred under Augustus and was largely confined to Italy; and only in A. D. 212 did Caracalla extend it to all of the adult male inhabitants of the Empire. Thus the census figures up to about 100 B. C. correspond to a constantly decreasing fraction, and those from 100 B. C. to the latest records correspond to an irregularly increasing fraction of the total population. The population data available are therefore so incomplete as to be useless for the present purpose.

As to the financial or monetary data, whether or not it be true that "wealth accumulates while men decay," it is demonstrably true that money depreciates in value as wealth increases; and the ancient data do not suffice to permit correction to a standard such as the "dollar of 1913" used by modern economists.

Again, the figures for numerical strength of the army are of little help, since it is evident that while the army increase corresponded in a general way to the conquest of territory, its sharpest increase occurred during the civil wars, especially in the period of Pompey and Caesar, Mark Antony and Octavius. After the latter had secured supremacy, he reduced the legions to about one-third of the peak strength of army total, and this sufficed for holding and expanding the Empire until the time of Septimus Severus.

In view of these deficiencies, it has been necessary to base the "power" curve of Ancient Rome chiefly on the territory curve, with some weight being given to the other three curves, and with estimated modifications where known historical occurrences definitely indicate a waning or waxing of strength not shown by the numerical data; but before considering these, the territory curve itself may be discussed.

While a "skew logistic" curve[5] could doubtless be fitted to a

[5] R. Pearl and L. J. Reed, "Skew Growth Curves," *Proc. Natl. Acad. Sci.*, vol. 11, (1925), pp. 16-22.

smoothed curve drawn through the stepped graph of territory, it was preferred to study how the latter is fitted by a simple symmetrical logistic curve of the form[6]

$$y = \frac{a}{1 + e^{-bt}}$$

The comparison is shown in Fig. 2, the logistic—curve (1)—being the curve corresponding to the expression

$$y = \frac{1}{1 + e^{-.0191\ (t + 60)}}$$

where t is the year of the Christian era (B. C. being negative). The curves here have been plotted in fractions of the area as of A. D. 120. If the area is to be expressed in square miles, the numerator of the fraction, or the constant a, becomes 1,898,000.

The logistic curve makes no provision for the period of decline, but from the mathematical standpoint this can be taken care of by regarding the decay phenomenon as an anti-growth feeding on the body of the empire (the anti-growth possibly representing either the growth of the congeries of barbarian kingdoms intruded into the empire, or as the growth of general anarchy at the expense of Roman order). Its curve will be a logistic with negative constant a, with a time-lag as regards the growth curve, and probably having a different growth-rate (different constant b). Also, evidently, the anti-growth cannot exceed, negatively, the maximum magnitude attained during the period of growth. The expression for the curve which fits the decline of the Roman Empire quite well—curve (2) in Fig. 2—is

$$y = 1 - \frac{1}{1 + e^{-.0366\ (t - 410)}}$$

and the entire life course of Ancient Rome, as regards territory, is fitted not too badly by the curve

$$y = 1{,}898{,}000 \left\{ \frac{1}{1 + e^{-.0191\ (t + 60)}} - \frac{1}{1 + e^{-.0366\ (t - 410)}} \right\}$$

The most conspicuous deviations of the stepped curve of actual area, from the logistic curve, are those appearing in the growth period, from about 100 B. C. to about A. D. 100. A mechanical analogy would

[6] Lotka, *op. cit.*, pp. 65-71.

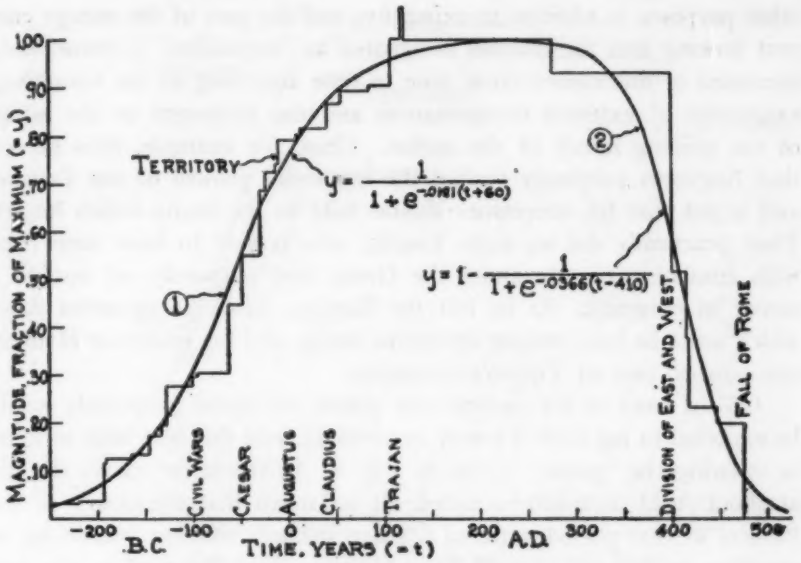

FIG. 2. COMPARISON OF SIMPLE LOGISTIC CURVES WITH ACTUAL GROWTH AND LOSS OF TERRITORY OF ROME

be that of a vibrating mechanism, in which it is known that "sticktion" or stick-and-slip friction can cause vibrations about the normal smooth path of motion, consisting of alternating overshootings and detentions.[7] Thus the halt after 100 B. C., following the civil wars, is noticeable, and is followed by a rapid rebound under Caesar, an overshoot under Augustus followed by a detention, and then a final overshooting under Trajan. (In living organisms, growth is known to proceed in some cases by fits and starts, or even by spurts followed by partial retractions, as in the spirogyra and the crocus, cited by Thompson.[8])

The territory curve, however, represents only an effect. What we are really interested in is national strength or "power," and this is partly a *cause* (or at least an agent) of expansion but is also partly a *result* of past expansion. Power probably grows according to a smooth

[7] W. Trinks, *Governors, Governing of Prime Movers,* New York (Van Nostrand), 1919, Ch. IX, par. 4.

[8] Thompson, *op. cit.*, p. 171, Figs. 39 and 40.

curve. Energy is available and is continually being transformed[9] for other purposes in addition to expansion, and the part of the energy current flowing into the channel designated as "expansion" is consciously increased or diminished from time to time according to the temporary exigencies of external circumstances and the judgment or the whim of the guiding minds of the nation. Thus, for example, it is known that Augustus purposely limited the territorial growth of the Empire, and urged that his successors should hold to the limits which he set. They practically did so, until Trajan, who is said to have been fired with emulation of Alexander the Great, and purposely set out on a career of conquest. As he left the Empire, its limits exceeded those which could be held without excessive strain, and his successor Hadrian relinquished part of Trajan's conquests.

On the basis of the concept just stated, territorial magnitude would be expected to lag behind power or strength, and this was kept in mind in drawing the "power" curve in Fig. 1. In the latter curve, the dip at about A. D. 240 will be noted. It is known that the power of the Empire at that period suffered a sharp decline, whether caused by or resulting in internal turmoil (six emperors were deposed in the first six months of the year 238) followed by irruptions of the barbarians. No data are available, however, for forming an accurate estimate of the magnitude of the decline in strength, which was not accompanied by any appreciable decrease of territory. An equally abrupt recovery occurred under the strong emperors Diocletian and Constantine, but again we have insufficient data for estimating the magnitude.

The dip in the curve at (4) in Fig. 3 could be represented by a curve (5) deducted from the general curve of decline (3). Curve (5) is of a form similar to that representing the growth and decline of a disease epidemic, and (4) can be considered as a premature decline followed by an arrest and partial recovery. In fact, for the whole period of decline, from about A. D. 160 to 475, it is probable that if sufficient data were available, the curve would be found to consist of a series of dips like (4). The historian, A. J. Toynbee,[10] who studied the rise and fall, not of nations but of civilizations (without using any statistical data, however), found that the average for some dozen civi-

[9] For the case of a living organism, this energy concept is set forth by R. Pearl in *The Rate of Living* (Knopf, New York, 1928) and by Thompson, *op. cit.*, p. 170.

[10] A. J. Toynbee, *A Study of History*, (Oxford University Press), 1934-39.

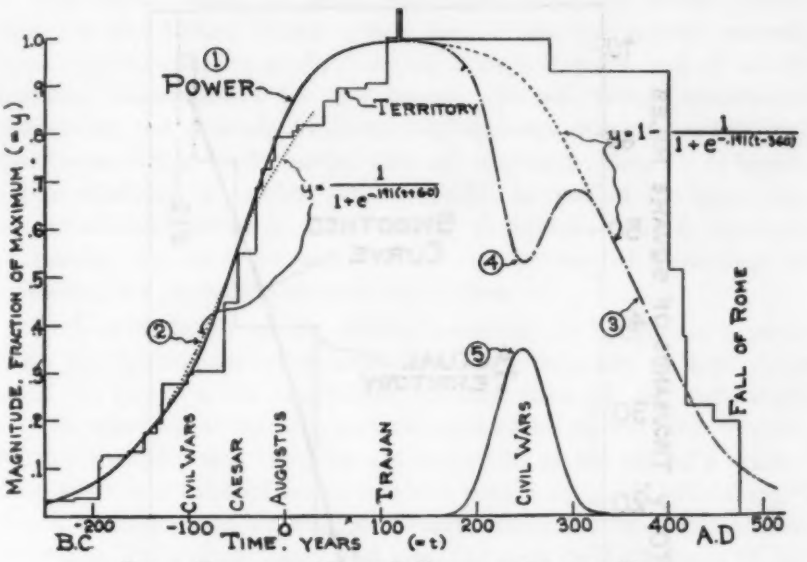

FIG. 3. ESTIMATED "POWER" CURVE OF ANCIENT ROME

lizations studied was 3½ waves of partial recovery during the entire decline.

Since in what follows we shall be dealing with the question of the possibility of prediction, or of extrapolating known, partially completed growth curves into the future, before leaving the study of Ancient Rome we may put to ourselves this question: if a Greek mathematician living in the earlier period of Roman expansion—say, Archimedes in 212 B. C.—had been able to obtain accurate figures on the increments of expansion of Roman-controlled territory for several centuries before that time (and had possessed the necessary mathematical equipment), would it have been possible for him to predict with any degree of accuracy the maximum magnitude which the Roman Empire would attain, and the time required for it to reach that magnitude? The answer must be in the negative, as consideration of Fig. 4 will show. The smoothed curve of territorial increase up to that time—which could be fitted only by a skew logistic curve (see footnote 5) corresponding to the equation

$$y = \frac{a}{1 + e^{(k_1 + k_2 t + k_3 t^2 + k_4 t^3 + \dots)}}$$

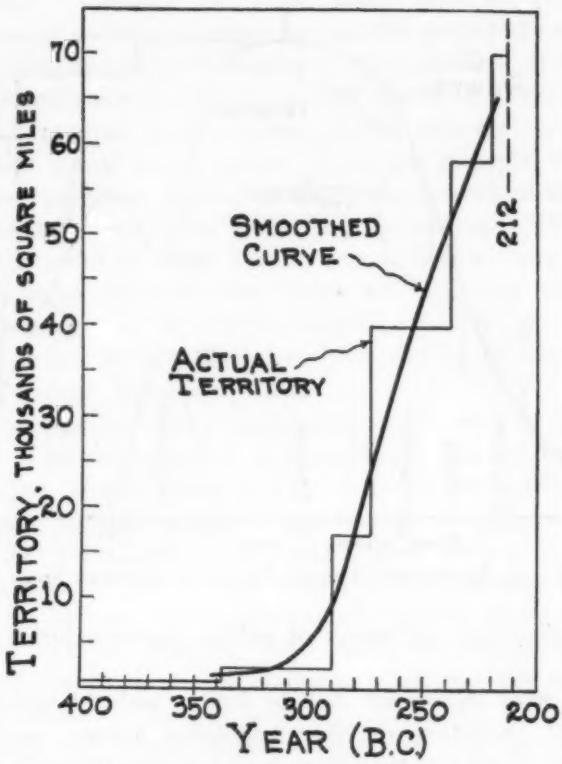

FIG. 4. TERRITORIAL GROWTH OF ROME, TO 212 B. C.

would have indicated that the inflection point had been passed, and that the curve although still rising rapidly had acquired an unmistakable droop. The maximum area, on the basis of this curve, would have been estimated at not over 200,000 square miles, and its time of attainment at probably 50 B. C.—or only about 10 per cent of the actual maximum area, and 160 years earlier in time than the actual zenith.[11]

* * * *

[11] That some of the more far-sighted Roman statesmen may have felt, in the time of Archimedes or within the following century, that Rome was approaching the end of her expansion, might be inferred from the fact that the younger Scipio changed the customary prayer for the enlargement of the republic into a prayer for its preservation, in 142 B. C.

The second nation, of which the growth is studied in the present paper, is the United States, which was chosen for several reasons. First, copious data are available in the Census Reports, and all of the historical circumstances are well known. Second, certain remarkable similarities, not generally realized, exist between our own nation and the Roman nation in the earlier part of its growth; these, it is hoped, can be discussed in another paper. Finally, in spite of the discouraging conclusion reached in the preceding paragraph, there is the hope of making the study of practical use in the way of estimating or predicting the probable future of our nation.

Such a study, of course, means venturing on dangerous ground. With the nationalistic spirit today having the intensity of a religious belief (in fact it *is* the real religion of most citizens), any such study may be regarded as impiety, and the student be classed with Wordsworth's scientific man, "peeping and botanizing on his mother's grave." This spirit is illustrated by an incident related by A. K. Weinberg.[12] About a century ago, an eminent French statesman, intending a compliment to the United States, had said, "If such be the infancy of the Republic, what will be its old age!" Senator Cass, one of the political worthies of the time, was highly indignant at this. "Sir," he orated, "it will have no old age!" At the present period, however, it may be considered more truly patriotic to face the facts, whatever they may be, and to utilize them for the guidance of the nation.

In obtaining the "power" curve for the United States in Fig. 5, a difference in conditions between our own and the Roman nation has been taken into account. While Rome expanded by conquering territory in most cases already fully populated, the United States expanded into almost empty territory. Hence its strength at any time was less than indicated by the territory, but greater than indicated by the population. As a first approximation, it seemed a fair procedure to draw a smoothed curve through the stepped graph of territory, and to take as the "power" curve the mean between this and the population curve.

As to territory owned by the United States, this has remained practically constant since 1898; and as to census population, the curve is known to have reached its inflection point about 1918, and is expected

[12] A. K. Weinberg, *Manifest Destiny*, Baltimore (Johns Hopkins Press), 1935, p. 217.

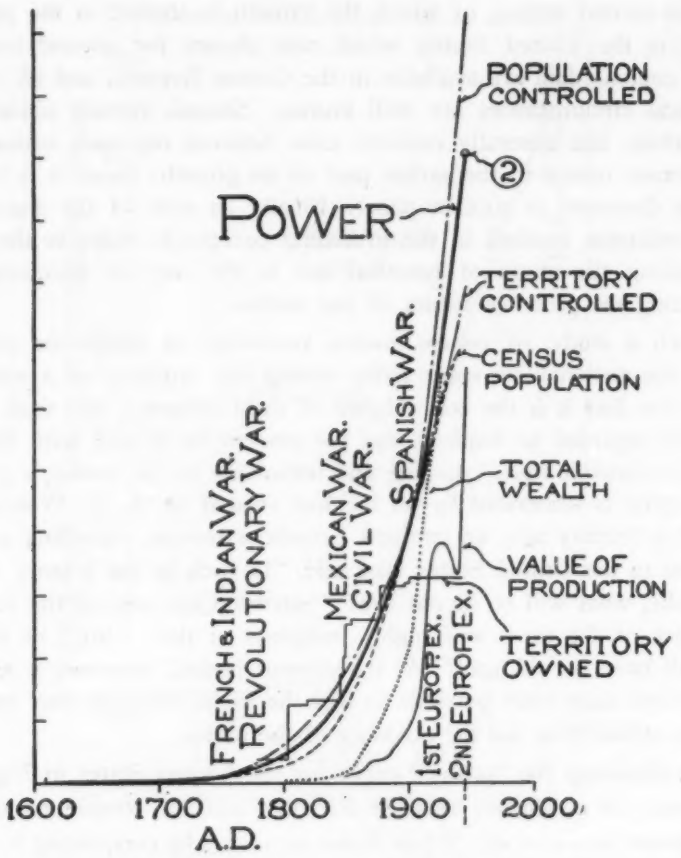

FIG. 5. GROWTH OF THE UNITED STATES

Scale of ordinates: Territory, 1 space = 1,000,000 square miles
Population, 1 space = 20,000,000 persons
Value of production (annual), 1 space = $20,000,000,000
Total wealth, 1 space = $50,000,000,000

to level off at not over 200,000,000, about A. D. 2000.[13] Considering only these two curves, the United States would appear to be at present approaching the zenith of its power, and to have not more than a century to go, before decline would be expected to set in.

[13] Lotka, *op. cit.*, p. 67, 68; also National Resources Planning Board, *Report* (1943).

Quite evidently, however, this presents a completely false picture; for, comparing the strength displayed by the United States in the war just ended as compared with its strength in 1917-18, it seems evident that in this period of less than thirty years the strength has at least more than doubled, whereas the population has increased only about 50 per cent and the formally owned territory not at all.

One factor which falsifies the picture is the concept—and fact—of "spheres of influence." Any modern Great Power has a group of satellite nations, which it does not own but at least partially dominates, and the resources of which add to its power. (To a lesser, but still considerable, extent, this was true also of Rome during its expansion in Italy as well as at a later period.) Hence it is not the nominal or formally owned territory alone which should be considered, but also the territory actually even if not formally controlled; and the same is true of population. For example, as regards the United States, it is evident that since the turn of the century we have been forming in the Pan-American bloc of nations the equivalent of Rome's Latin Confederation; and that at the present time the United States half-controls both territory and population[14] almost to the Bulge of Brazil. Further south, the Argentine Republic sets itself to remain independent of us, playing against us Britain, formerly Germany and now Russia, while our government with equal tenacity works to bring Argentina also within our orbit.

Just what weight should be assigned to these associated nations as a factor in our national strength, is highly uncertain. As a first approximation, "half-control" (the "half" itself being but a rough estimate) was equated to "control half," and to obtain the controlled-population and controlled-territory curves in Fig. 5, half the values for the Central and South American countries as far as the Bulge of Brazil were added to the figures for the population and territory formally owned by the United States. On that basis, our "power" curve is still rising rapidly and has not yet reached its inflection point.

* * * *

[14] How omnipresent this indirect control is, has been brought out in the writings of the South American intellectual, Manuel Ugarte.

Assuming the growth curves for Ancient Rome and for the United States, derived on these different and admittedly quite uncertain bases, to be approximately correct, and also assuming that the parallelism of the two "power" curves will continue throughout their course, an attempt was made to determine to what period of Roman growth the present point on the growth curve of the United States corresponds. This was done in the following way. On semi-logarithmic charts, the growth curves of the United States and of Rome were plotted, the latter with the 100 per cent point taken at three different years thirty years apart, namely 180, 150, and 120 B. C. Comparing Fig. 7 for Rome with Fig. 6 for the United States, it will be seen that in the

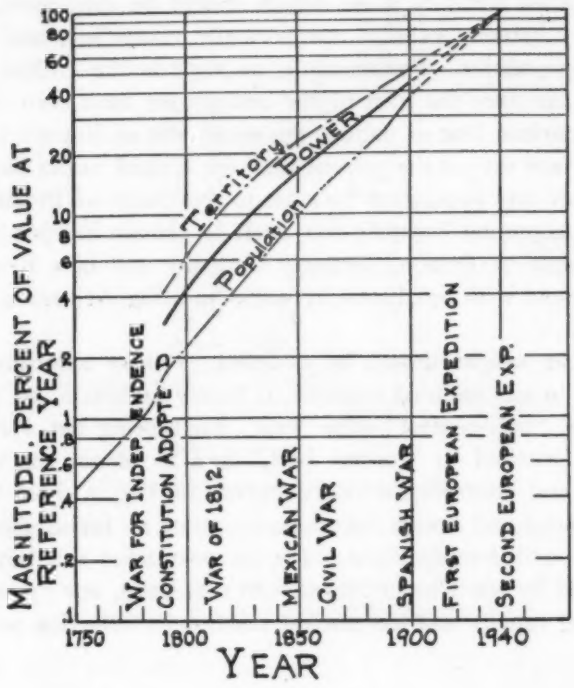

FIG. 6. SEMI-LOGARITHMIC CHART OF GROWTH OF THE UNITED STATES

upper range the curve for the United States is practically a straight line; for Rome, based on 120 B. C., the curve has a decided droop, while the curve based on 180 B. C. has a slight upward concavity. The

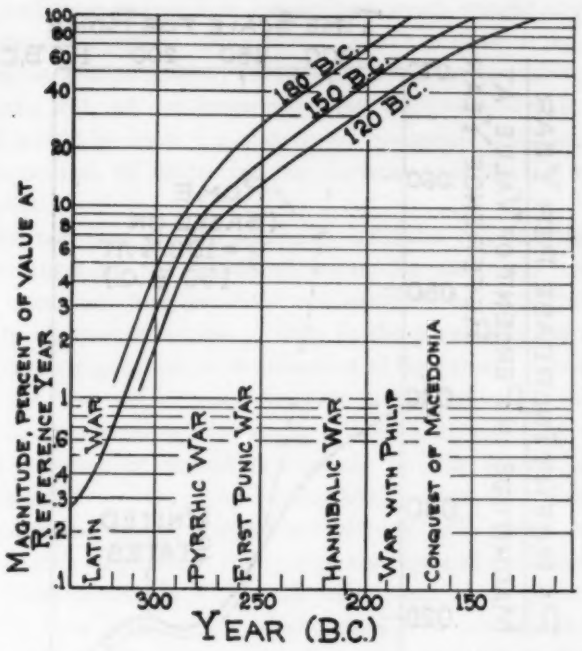

FIG. 7. SEMI-LOGARITHMIC CHART OF GROWTH OF ANCIENT ROME

curve for 150 B. C. in Fig. 7 is seen to be the most similar in form to the "power" curve of the United States in Fig. 6.

As a check, the *slope* of the "power" curves in Figs. 1 (or 3) and 5 was measured (see Fig. 8), representing the percentage increase per year. While it is recognized that the probable error of a curve thus obtained by mechanical differentiation is much increased as compared with the original curve, nevertheless the general similarity both in form and in magnitude of the slope curves for the United States and for Rome, when the latter is based on the correspondence of 150 B. C. for Rome to 1942 for the United States, is believed to confirm the conclusion reached on the basis of comparison of Figs. 6 and 7.

Incidentally, it seems quite remarkable that in spite of the wide differences between ancient and modern times as regards speed and ease of transportation and communication, the slope of the curves, or the growth rate based on percentage increase per year, is almost exactly the same for the United States as for Ancient Rome.

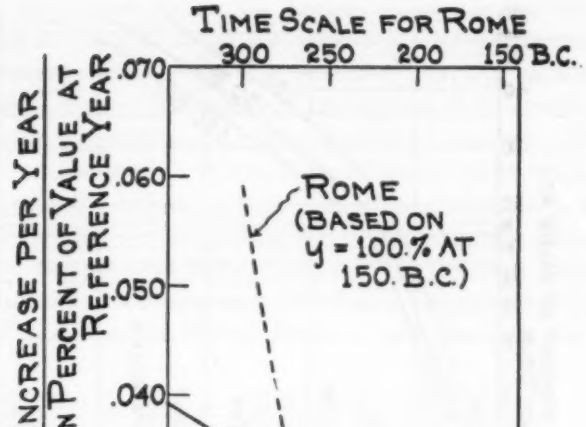

FIG. 8. COMPARISON OF SLOPE OF GROWTH CURVES

Having identified at least approximately the present position of the United States in its growth curve (point (2) in Fig. 5 corresponding to point (2) in Fig. 1), if one could be reasonably sure that future growth will follow the same form of sigmoid curve as in the case of Rome, then it would not be too rash to venture a prediction. On that assumption, our nation (or empire) would be expected to reach the zenith of its power about A. D. 2200, with a magnitude of six to seven times that of the present United States. But as pointed out by Professor G. E. Hutchinson, mere parallelism, admittedly imperfect, hard-

ly admits prediction unless it is known how much weight should be assigned to the divergencies between the curves at time t_1 in predicting the relations at a later time t_2. It may be the most probable prediction in the present state of our knowledge, but the probability is still quite low. What would be needed is a study of numerous additional cases of national expansion, to determine the variations in the form of their growth curves.

Also, the fact that growth occurs by irregular fits and starts makes the determination of the smoothed curve for the early part of the growth so uncertain, that any bold extrapolation of it is likely to lead to extremely inaccurate results, as seen in the previously stated case of a hypothetical extrapolation by Archimedes of the growth curve of Rome.

Finally, in the author's opinion the magnitude and the rate of future national expansion are largely (though certainly by no means entirely) a question of conscious control. In this respect, of course, a nation differs from even the higher living organisms, but evidence for such conscious, willed control has already been stated in the case of Rome. In this connection, the energy concept and the conclusions of Raymond Pearl from his studies of insect and plant growth, are of great interest (see footnote 9). Pearl states, *"In general, the duration of life varies inversely as the rate of energy expenditure during life."* If this applies also to nations, some at least of our citizens would be glad to compound for a great increase in length of life of the nation even at the expense of proportional limitation of the nation's expansion. Others would doubtless say with Tennyson, "Better fifty years of Europe than a cycle of Cathay," and would prefer that the nation live the strenuous life, expend its energy for expansion unlimited, and go out in a blaze of glory.

Strangely enough, Pearl found in his studies of plant seedlings that the maximum magnitude attained was almost the same whether the growth was slow or fast. But in the case of a nation, one feels (without having any definite proof) that the area under the growth curve for the full cycle of growth and decline must be proportional to the energy available; that for a given nation the latter is fixed in amount (Pearl's "inherent vitality"); and that consequently, an unduly rapid growth to much greater than average size must be followed by correspondingly rapid decay and disintegration. This conclusion is confirmed in a general way by the history of other empires such as the Spanish and the Turkish.

The present study, tentative and sketchy as it is, will have served its purpose if it interests others to make a more thorough study of these or other national growths.

A STUDY OF FETAL MOVEMENTS IN RELATION TO MOTHER'S ACTIVITY

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FETAL behavior has been studied chiefly by the application of specified stimuli, mostly tactual, to operatively delivered organisms, both human and infra-human. A number of attempts have been made to modify spontaneous fetal activity *in utero* by the conditioned reflex method, using stimuli external to the mother. Only a few studies exist to show in man the effect of the mother's normal routine on the fetus' activity.

Interest in the general problem of intra-uterine fetal behavior dates back to 1880 when Hicks (1) devised a pneumatic tambour to record fetal movements. In 1932, Ray (3) used three, two-inch tambours to record such movements in a conditioning experiment, locating them over different parts of the fetus. Later, Sontag and Wallace (8) devised an improved pneumatic method consisting of four air sacks shaped to form four quadrants of an ellipse. These air sacks were placed adjoiningly over the abdomen and covered by a previously prepared thin plaster cast in order to make them conform to the body. A method recently reported by Kellogg (2) abandons the pneumatic principle. Two abdominal plates of 28 gauge sheet metal, two and one-half inches wide and 8 and 16 inches long, respectively, curved to fit the abdomen, are placed transversely of the longitudinal axis of the mother's body, the shorter one nearer the pelvis. Six and one-half inch vertical rods soldered to the center of the plates translate lateral movements of the plates, induced by fetal activity, into tracings on a kymograph drum. A simple adjustment of the plates completely eliminates from the kymograph record any vertical movements of the rods induced by mother's breathing and it is claimed that "no fetal response of sufficient magnitude to move the abdominal wall .02 inch or more would fail to produce a slight deflection in the record line." Along with the mechanical record, Kellogg obtained verbal reports of activity from his subject.

Several studies have used mother's report of fetal movement. Richards, Newbery and Fallgatter (4) obtained from 1 to 17 records from each of 17 mothers during the last 20 weeks of pregnancy. These mothers reported at the laboratory weekly or bi-weekly at 9 or 9:30 a. m. and remained until 2:30 or 3:00 p. m. During this time they remained in bed, read, sewed, manicured, smoked or conversed. Lunch was served to them in bed. Fetal movements perceived by the mothers were recorded by pressure on a button, actuating a writing pen. Another button recorded changes in the mother's activities, the number of pressures indicating the new activity by a prearranged code. The authors used a score which indicated "minutes active per 10 minute interval" rather than number of movements perceived. A correlation of $.93 \pm .015$ between these two types of scores led the authors to the conclusion that the former, more easily derived score was a reliable indication of the variable actually under study.

Schmeidler (5) established introspective records on fetal twins, most of her observation periods being an hour in length. Thirty-three observations covered the period of the 23rd to the 31st week of fetal life. The first 15 observations appeared to show some relation to maternal activity preceding the session; consequently, during the final weeks of the study, one observation period was held prior to rising in the morning and another after one hour of normal activity. The number of movements was estimated on a five-point scale, and a brief general record of data of conditions preceding the session was kept.

Efforts in these studies to trace some relationship between mother's activity or condition and amount of fetal movement are in many instances inconclusive. Sontag and Wallace (8) in describing a proposed research program of the Fels Institute refer to general clinical evidence, and to testimony of their subjects that states of marked fear or conditions of prolonged emotionality appear to increase fetal activity. An experience of extreme fatigue likewise appears to be associated with more frequent and more violent fetal movements.

Sontag and Richards (7) obtained a measure of fetal heart rate by timing ten-beat intervals with a stop watch, and recording them over periods of minutes. While heart rate variations were at a minimum during quiet periods of the fetus, there was a marked fluctuation within very short periods during intervals of activity. The authors conclude that "on the whole heart rate is greater during minutes wherein activity occurs," but their data indicate this to be only a very slight tendency.

Since heart rate is merely an indirect measure of overt activity, the use of heart rate as a measure of fetal movement does not seem justified. Various forms of stimulation applied to the person of the mother, such as smoking, eating, and rest, did not yield definite effects. A vibrator stimulus applied to the mother's abdomen produced acceleratory effects on both fetal activity and heart rate (the latter presumably as a consequence of the former) in all cases. The authors have the following to say concerning the relative merits of mother's report and instrumental recording of fetal activity:

> "The mother's report of movement has been found to be as accurate a measure, and possibly more sensitive; yet the objection validly may be raised that mothers may vary in their uterine sensitivity, due to physical factors of sheer size and position and muscular tension, and to the possibility of individual differences in the threshold of sensitivity, which we might expect from other measures of sensory phenomena. This is, indeed, quite possible, but it does not entirely invalidate the method, if precautions are taken in interpreting the results thus secured." (p. 2)

> "The mother in almost all cases was asked to report fetal movement when she noticed it. This was found to present as great or greater incidence of activities than did the use of the direct recorder described in an earlier publication." (p. 8)

The study by Richards, Newbery, and Fallgatter (4) deals more directly with fetal activity itself. The authors show that for 17 subjects the average number of minutes active per ten minute period increased steadily through the later months of pregnancy, but decreased in the tenth month. They fail to find any relation between fetal activity and kind of activity the mother engaged in, concluding that their activity categories were possibly too broad to show a relationship. No correlation of fetal activity with hour of the day was observed. While there was no significant correlation between mother's basal metabolic rate sampled during later months of pregnancy and amount of fetal activity, there was a significant rank order correlation (rho $= .60 \pm .11$) between fetal activity and amount of increase in mother's metabolic rate from a measure taken early in pregnancy. The authors conclude that "both BMR and fetal activity measures are indicators of heightened metabolism of the mother-child unit." The rank order of fetuses in amount of activity was fairly constant throughout the last four or five months of pregnancy, but there was no relation between level of activity and size at birth. The mean heart rate and the mean percentage

of time active during the same period yielded a rho value of $-.22 \pm .17$, which is insignificantly larger than zero. This finding does not agree with the statement of Sontag and Richards (7) that increased heart rate tends to accompany increased fetal activity.

Schmeidler (5) found that fetal activity increased with fetal age and that maternal activity or fatigue decreased the number of perceptible fetal movements which occurred in the first half-hour after such activity. Movements following a period of maternal activity were at a minimum immediately after that activity and increased steadily throughout an hour of quiet observation. The inhibitory effect of mother's activity or fatigue was attributed to an accumulation of toxins in the maternal blood stream.

Kellogg (2) defined a fetal movement as an excursion of the writing point on the kymograph record in excess of a certain arbitrary amount. As thus defined, the average number of movements per minute increased throughout the time observed, but showed a decrease in the tenth prenatal month. The number of movements recorded by the subject as introspectively perceived were far fewer than the objectively defined movements. The number of discrete and separable periods of activity experienced by the mother decreased with fetal age, and length of period increased from about four to 33 seconds. From observation to observation, there were considerable differences in the amount of movement in both objective and subjective accounts.

Kellogg (2) recognized two possible sources of error but discounted the seriousness of both. Smooth muscle contractions of the uterus were slow and could be clearly differentiated from fetal movements on the record. The effect on the writing point of contractions in the amniotic sac was undetermined, but the contractions were believed to be slow and of slight intensity.

In none of the studies here reviewed were the records as complete as could be wished. Few attempts to control or to vary systematically the mother's schedule were made. Observational method and kind of record have varied considerably from study to study, which prevents direct comparisons of results. Of course, in the early stages of investigation, there needs to be study of appropriate method as well as of the phenomena itself, and it is clear that a wholly satisfactory technique must yet be devised.

Difficulties in the treatment of such data are many. The quantitative increase in the variable measured complicates the problem of statistical

method. Qualitative changes as well as shifts from brief movements to movements much more extended in time and space are difficult to treat quantitatively. Qualitative descriptions are limited by lack of a precise descriptive vocabulary and by the subjective nature of the phenomenon observed.

THE PROBLEM

The present study of fetal behavior was designed to answer several questions: (1) Does a thirty-minute subjective observation yield a statistically reliable measure of fetal activity? (2) Is there any apparent relation between mother's experienced fatigue and amount of fetal activity? (3) Is there any relation between hour of day and amount of fetal activity, between day of week and amount of fetal activity, on the assumption that hour of day or day of week might systematically affect mother's activity? (4) What is the relation of length of mother's day to amount of fetal activity at night, of number of hours in bed to amount of fetal activity at rising?

METHOD

Time sampling observations of fetal activity were made each day for thirty consecutive minutes prior to the mother's rising and for thirty consecutive minutes after her retiring. All observations were made by the mother herself while reclining with head and shoulders propped on two pillows. A stop watch running continuously for the 30-minute period was placed in easy view. The record form was a sheet of squared paper attached to a clip board, a line of 30 squares being devoted to one observational period. Each clearly perceptible and separate movement or kick was recorded by a pencil stroke in the proper square. A small circle indicated doubtful movements which were usually of very faint intensity. A continuous movement extending from one position of the abdomen to another was recorded as one movement. Very rapid, rhythmical pulsations of constant intensity which infrequently occurred, particularly during later periods of the study, were indicated but ignored in the statistical tabulation, as their count was unreliable. Time of beginning the observation was recorded and the subject's general feeling of well-being or fatigue estimated by the following four-point scale:

1. Rested
2. "Neutral"
3. Tired
4. Very fatigued

An effort was made to follow Schmeidler's plan for recording the location of movements, but this was abandoned as too uncertain and as likely to reduce the reliability of detection of movement.

The daily observations on the fetus began on May 20, 1941, at 138 days of menstrual age, six days after first perceptible movements occurred. These observations continued for 129 days, with the exception of four morning and six evening records, and terminated approximately 36 hours before birth of the infant.

Only the records of perceptible movements were used in tabulations. Time of observation was recorded as of the nearest clock-hour or half-hour; thus, any period beginning at 15 minutes before the clock hour to 15 minutes after the hour was recorded as of that clock hour and similarly for half-past the hour. In the statistical analyses, morning and night records were treated separately.

QUALITATIVE OBSERVATIONS

During the first 30 days of observation, there were about as many uncertain as certain movements recorded. Thereafter, the uncertain movements tend to disappear from the record. On the whole, the uncertain movements tend to scatter, and not appear in "runs" or clusters. The rhythmic palpitations previously mentioned were most likely to develop during the 8th, 9th, and 10th months and would occur on some occasions over a period of several minutes and at other times only for a part of a minute. They were equally likely to develop in morning and in evening periods. It is possible that this phenomenon of light, rapid pulsations of constant intensity is similar to Schmeidler's "ripple movement" which she observed in the later months of pregnancy and found so difficult to classify as one or several movements. The subject experienced no particular difficulty in recording movements as continuous or separate in time.

RESULTS

The "reliability" of the observations was estimated by finding Pearson product-moment values between the sums of movements oc-

curring in odd-versus-even minutes of the observation periods. Thus, in the correlation scattergram the entry on the ordinate would consist of the sum of all movements occurring in even-numbered minutes of the observation period, while the entry on the abscissa would consist of the sum of movements in the odd-numbered minutes. The resulting correlation coefficients given in Table 1 are quite high, and could result

TABLE 1

Reliability coefficients; record of fetal activity in odd versus even minutes of observation

NUMBER OF OBSERVATIONS		RELIABILITY COEFFICIENT
A. M.	First 30 records	.84
	Next 69 records	.71
	Final 36 records	.49
P. M.	First 30 records	.75
	Next 69 records	.83
	Final 34 records	.80

only if two conditions were fulfilled: (1) the variation of total amount of movement occurring in any one observation period is considerable from period to period, and (2) within any one thirty-minute period, the variable as observed is reasonably stable. Considering the subjective nature of the data, the "reliability" figures probably indicate reasonably consistent performance of the observer, since few biological phenomena vary erratically over short intervals of time. A tendency for the reliability of morning observations to decline in middle and later weeks of the study is not observed in the evening data. Thus, it would appear that the statement made in other studies, that mother's account of activity may be taken as an accurate estimate, is supported by quantitative procedure.

The raw data of this study, consisting of totals of perceived movements for 30-minute observation periods, are plotted in Fig. 1. Four facts are at once apparent: the very considerable sample to sample variation of fetal movement, which lasted throughout the prenatal period studied, a rather rapid rise of the curves for both morning and evening observations to a characteristic level of activity after about one month of perceived movement, the considerably greater activity

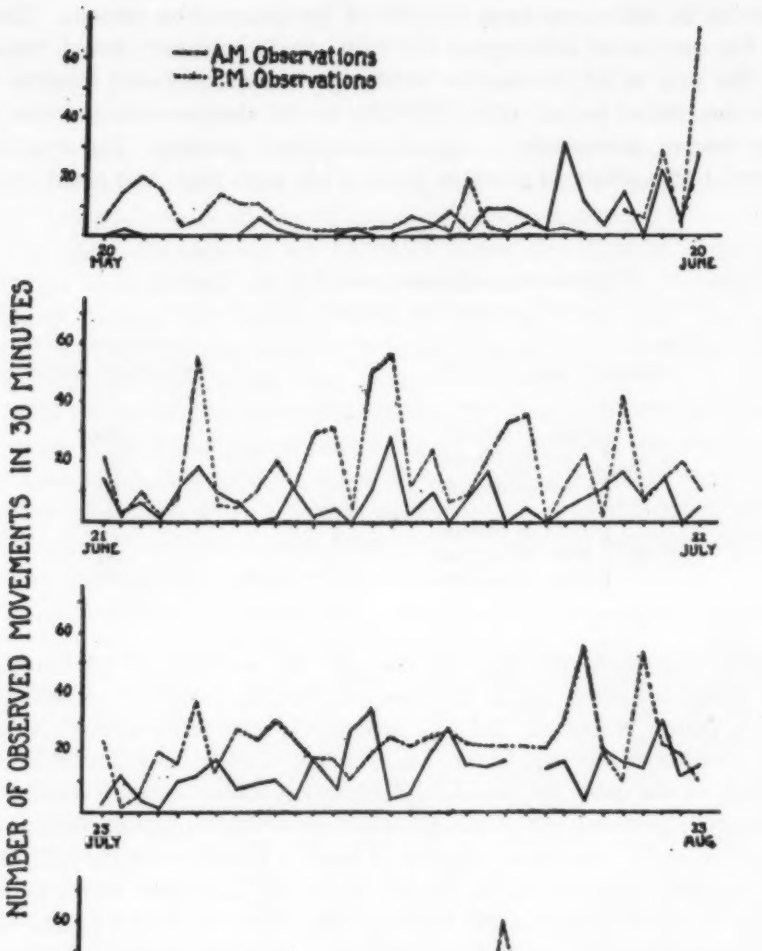

FIG. 1. TOTAL OBSERVED FETAL MOVEMENTS IN 30-MINUTE PERIODS ON SUCCESSIVE DAYS

evidenced in the evening periods, and the absence of concomitant variation in morning and evening records.

Table 2 reduces the data of Fig. 1 into descriptive statistics for 15-day periods. The general observations cited above are more clearly delineated. The tendency to reduction in fetal activity, noted in obstetrical experience and in the Richards, Newbery and Fallgatter, the Schmeidler and the Kellogg studies during the last weeks of pregnancy, is not apparent in these data as a statistically reliable trend.

TABLE 2

Mean number of movements per observation, and standard deviations, calculated from records of fetal activity for consecutive 15-day intervals

DATES	MORNING OBSERVATIONS			EVENING OBSERVATIONS		
	Number	Mean	S.D.	Number	Mean	S.D.
May 20—June 3	14	0.6	1.4	15	7.6	6.5
June 4—June 19	16	7.8	8.2	15	5.6	7.6
June 20—July 4	15	7.6	7.7	15	18.7	20.0
July 5—July 19	15	8.3	7.7	15	22.1	17.7
July 20—August 3	15	8.5	5.6	15	18.8	9.5
August 4—August 18	14	15.2	8.7	14	23.2	9.8
August 19—September 2	15	15.4	6.4	15	24.1	13.8
September 3—September 26	21	12.1	7.7	19	23.4	13.6

The relationships between fetal movements and day of week, hour of day, and rating of fatigue, respectively, were studied by comparing average movements for each category of the factor studied. The averages were based on 30-day rather than 15-day periods to increase reliability of the means, without prejudicing them too much from long-time trends inherent in the variable itself. Scrutiny of these data failed to reveal perceptible trends or patterns of relationships among the various mean values. Table 3 summarizes the results of variance analyses applied to these data. Means of movements in the morning observation periods computed for the days of the week vary significantly[1] only

[1] The criterion of statistical significance is set at the $P = .01$ level; when the probability of finding a variation among sub-sample means is only .01 or less, the differences can logically be attributed to factors other than errors of sampling.

TABLE 3

Results of the analysis of variance, data classified by days of week, by hours of day, and by fatigue categories

(Note: The symbol "—" indicates $P > .05$; "s" indicates P is between .05 and .01; "S" indicates $P < .01$.)

PERIOD	BETWEEN MEANS OF DAYS OF WEEK	BETWEEN MEANS OF HOURS OF DAY	BETWEEN MEANS OF FATIGUE CATEGORIES	BETWEEN PERIODS
A. M.				
May 20 — June 19	—	S	—	
June 20 — July 19	—	—	—	
July 20 — Aug. 18	s	—	—	
Aug. 19 — Sept. 26	S	—	s*	
Entire period	s	—	—	s
P. M.				
May 20 — June 19	—	—	—	
June 20 — July 19	s	—	—	
July 20 — Aug. 18	S	s	s	
Aug. 19 — Sept. 26	s	—	S	
Entire period	—	—	—	s

* The elimination of one deviant observation would increase the probability beyond the .05 to .01 category.

for the last five weeks (August 19 to September 26), and means for hours of the day only for the first four weeks (May 20 to June 19). Inspection of the original tables showed that in the periods referred to, Sunday and Wednesday are days in which the average amount of movement is appreciably less than on the remaining days of the week. Observations made at 8 a. m. yielded less activity on the average than those made at 6, 7, or 9 a. m. The analyses of evening observations are likewise puzzling. Means of fetal activity vary significantly for days of the week only in the period from July 20 to August 18, while hours of the day do not show differences between means reaching the $P = .01$ level. Tuesday, Thursday, and Friday are days of little activity in the evening as compared to other days. Only during the last five weeks does fatigue rating relate to fetal activity; extreme fatigue is associated with significantly less activity than is moderate fatigue.

Although Table 3 suggests that day of week may be a factor in producing different levels of fetal activity, the days of heightened or lessened activity change from period to period. These findings correlate with no recorded or remembered facts concerning systematic variation of mother's program at or just prior to these times.

It must be remembered that the grouping of observations into four-week intervals is a wholly arbitrary procedure. In a different plan of grouping, "significant" differences might drop below the accepted level, or other significant differences might appear. That day of week should be (presumably) important in relation to fetal activity in one arbitarily designated four-week period and not in three others, and that hour of day should be important at one interval of fetal development and not at others, may work out statistically, but in the absence of clearly associated extraneous factors, it is probably safest to state that these instances are the more unlikely "chance" deviations of samples from a true mean. Replications of this study would be needed, however, to "verify" this hypothesis.

In this connection, it is interesting to note that for both morning and evening observations, the means of activity for the four 30-day periods taken separately only approach and do not reach the $P = .01$ level of significance by the analysis of variance procedure. Yet Table 2 clearly shows a trend for the same data broken into 15-day intervals. Possibly greater experimental control of conditions preceding observations and of the time spacings of the observations, would yield positive results.

In no instance does the variance technique applied to all the observations for the day, hour, or fatigue rating factors, indicate differences among means reaching the $P = .01$ level. One may legitimately ask whether an interaction of two of the above factors might not yield results too discrepant to be assigned to sampling errors. The variance method devised to treat data classified simultaneously by day of week and hour of day, for example, has been described by Snedecor (6) as the method of expected or proportional subclass numbers and is an adaptation of methods properly applicable to material experimentally randomized with respect to the factors of classification. Such statistical adjustments are actually makeshifts for inadequate experimental or observational variation, and results of such analyses must be accepted with reservations.

Tables 4 and 5, for all evening observations, fail to show that variance attributable to day means, or to hour means, or to day-hour interaction is significantly greater than the error variance. The variance attributable to means of days of week, while it is short of the $P = .01$ level, does fall at about the $P = .04$ level. The analysis in Table 5 re-

TABLE 4

Variance analysis of evening observations, data classified by day and hour

SOURCE OF VARIATION	D. F.	MEAN SQUARE	F	P
Between means of day-means	6	49.9	.18	$> .05$
Between means of hour-means	3	238.8	.85	$> .05$
Day-hour interaction	18	393.0	1.40	$> .05$
Error	95	279.0		

TABLE 5

Variance analysis of evening observations, data classified by hour and fatigue rating

SOURCE OF VARIATION	D. F.	MEAN SQUARE	F	P
Between means of hour means	3	155.1	1.01	$> .05$
Between means of rating-means	2	20.2	.13	$> .05$
Hour-rating interaction	6	438.2	2.86	$.05 - .01$
Error	111	153.4		

lates to classification of the evening data simultaneously by hour and fatigue rating. Here, the variance attributable to hour-fatigue interaction exceeds the $P = .05$ level, but falls short of the $P = .01$ level, with respect to the error variance. Inspection of the original data suggests that late hours of retiring in relation to considerable fatigue may be related to reduced fetal motility.

Schmeidler (5) found a definite reduction in fetal activity with increased maternal activity and fatigue and advanced an hypothesis based on the presumed inhibitory effects of fatigue toxins present in the mother's bloodstream.

But the results of the present study with respect to mother's fatigue need further scrutiny, for if one assumes (as he would ordinarily) that a person is more fatigued at the end of a day than at its beginning, how will he explain on the basis of a fatigue hypothesis the consistently *greater* fetal activity in the evening as compared with morning observations throughout the study? (See Table 2.) And Table 6 shows very little overlapping of distributions of fatigue ratings for the morning and evening periods. Forty-one of the 74 "very fatigued" ratings occurred in the last 56 records, when the fetus had assumed noticeable weight and proved an uncomfortable burden. Certainly the mother's psychological experience of fatigue was greater at the end of day.

TABLE 6

Distribution of fatigue ratings of morning and evening periods of observation

RATING	MORNING	EVENING
Rested	92	—
"Neutral"	29	7
Tired	2	42
Very fatigued	1	74
Total	124	123

One possible explanation to account for greater evening fetal motility relates to mechanical disturbances induced by the erect posture and activity of the mother during the day in contrast with conditions of rest in bed. This hypothesis may be accepted tentatively and extended to state that a long waking day for the mother should prove more "disturbing" to the fetus than a short day, and the converse with respect to hours in bed. The morning and evening observations of a given day or days were considered in pairs to yield the pertinent information. This analysis was applied to data from 60 consecutive days covering the seventh and eighth prenatal months, approximately.

First, does the number of hours in bed show any association with the movements recorded in the morning observations following? The mean value of Table 7 suggests that there is little difference in fetal activity following six to nine hours in bed; there is some indication that

longer hours in bed may be associated with greater fetal activity. Second, is a long day associated with more or less fetal activity during the

TABLE 7

Mean fetal movements per observation, following various periods in bed or active during the day

	HOURS IN BED						HOURS ACTIVE DURING DAY				
	6	7	8	9	10	11	13	14	15	16	17
Number	4	7	16	14	15	4	7	15	14	16	6
Mean	8.5	7.8	8.1	9.4	11.5	18.0	23.6	14.9	22.3	23.6	17.3

evening hours of observation? Table 7 reveals no consistency of trend among the averages for different lengths of day.

Table 8 shows a tendency for less activity to be associated both with greater feeling of rest and fewer hours in bed. Table 9 shows that a

TABLE 8

Mean number of movements observed in the morning: data classified according to number of hours in bed and rating of fatigue upon arising

RATING ON ARISING	HOURS SPENT IN BED			
	6, 7, 8		9, 10, 11	
	N	M	N	M
Rested	18	7.7	30	10.8
Neutral	9	9.0	3	17.0

greater experience of fatigue at retiring is clearly associated with longer days but that the interrelationship of length of day and degree of fatigue, and amount of movement is contradictory. Being tired at the end of a shorter day is associated with greater average motility than being tired at the end of a longer day. On the other hand, being very fatigued at

TABLE 9

Mean number of movements observed at night: data classified according to number of hours active during the day and rating of fatigue upon retiring

RATING UPON RETIRING	HOURS ACTIVE DURING THE DAY			
	13, 14		15, 16, 17	
	N	M	N	M
Tired	12	22.2	9	16.6
Very fatigued	10	12.3	27	23.9

the end of a short day is associated with *less* movement than being very fatigued at the end of a *long* day!

At the risk of further complicating the comparisons, we may raise still another question: What relationships appear between the ratings of fatigue at bedtime, the number of hours in bed, and the amount of fetal activity observed in the morning? Table 10 shows that greater morning activity tends to be associated with longer periods in bed, but that being very tired at night is associated with no greater movement in the morning, regardless of number of hours spent in bed. (The median number of hours spent in bed is the same for both "tired" and "very fatigued" ratings at retiring.)

What relationships appear between the rating of restfulness experienced at rising, the length of day, and the amount of activity observed in the evening? The data of Table 11 fail to show trends of any sort.

To summarize, it has been shown that a subject can make reliable observations of fetal movements without the aid of special equipment. In this study, fetal movements were recorded for 30 seriatim one-minute observational periods prior to arising in the morning and for a similar set of observations just after retiring at night throughout the period of pregnancy following first noted movements. Movements increased in strength and number most rapidly during the first month of perceived motility. The fetus was consistently more active at the close of the observer's day, but there was no concordance in relative number of movements observed, morning and night.

With respect to the effects of fatigue on fetal action, the study is less conclusive. Either as rated or inferred from long or short days,

TABLE 10

Mean number of movements observed in the morning: data classified according to rating of fatigue upon retiring and number of hours in bed

FATIGUE RATING UPON RETIRING	HOURS IN BED			
	6, 7, 8		9, 10, 11	
	N	M	N	M
Tired	14	8.6	8	13.4
Fatigued	28	8.3	10	13.4

TABLE 11

Mean number of movements observed at night: data classified according to rating of fatigue upon arising, and number of hours active during the day

FATIGUE RATING UPON ARISING	HOURS ACTIVE DURING DAY			
	13, 14		15, 16, 17	
	N	M	N	M
Rested	20	19.0	26	18.5
"Neutral"	2	11.5	10	21.9

mother's experienced fatigue cannot be said with assurance to be associated with fetal activity. During the latter weeks of pregnancy, in the evening hours, the mother noted less movement on the days of her greatest fatigue. This finding agrees with the general conclusion of Schmeidler (6). But the effect of fatigue is considerably less than the effect of some unknown factor operating to *increase* activity during the mother's active and fatiguing day.

An effort was made to locate this factor in the upright posture and bodily activity of daytime as contrasted with the reclining posture and relaxation of sleep. Sixteen hours of erect posture and activity had no more acceleratory effect on fetal motility than a shorter day of 13 or 14 hours; if the mother's daytime posture induces greater fetal activity, the effect is fully apparent in less than 13 hours.

In relation to length of day, or to length of night sleep, degree of experienced fatigue or rest showed no consistent relation to amount of fetal motility. The familiar generalization about the constant nature of the fetal environment remains unchallenged by this study.

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NOTES

PROBABILITY OF DEATH AND EXPECTATION OF LIFE

IT HAS been shown by Dr. B. D. Karpinos in a recent article[1] that a division of all probabilities, q_x, by a common factor k does not result in a multiplication of $e(o)$ by the same factor. Here, q_x stands for the probability of dying within one year, and $e(o)$ is the expectation of life of a newborn. The proof given by Dr. Karpinos is purely numerical. He considers different U. S. life tables and shows that the same change in the probabilities, q_x, leads, for different life tables, to different changes in the expectations.

His result (without the numerical precisions) may also be obtained from the following *a priori* reasonings:

The probability $l(x)$ to reach an age x is

$$l(x) = \prod_{o}^{x-1} (1 - q_x)$$

and the expectation of life of a newborn is

$$e(o) = \int_{o}^{\infty} l(x)\, dx$$

Now, let a second life table be

$$l_1(x) = \prod_{o}^{x-1} (1 - k\, q_x), \text{ with } k > 0.$$

Then we cannot expect that the corresponding expectation $e_1(o)$ is

$$e_1(o) = \frac{e(o)}{k} \tag{1}$$

except under very restrictive analytic conditions.

---

[1] HUMAN BIOLOGY, Vol. 18, No. 2, 1946.

The equality (1) holds if the probability $q_x = q$ is independent of the age x. This means that the life table is an exponential function

$$l(x) = e^{-\frac{x}{e(o)}}$$

or that the probability $q_x = 1 - \dfrac{l(x+1)}{l(x)}$ is

$$q = 1 - e^{-\frac{1}{e(o)}}$$

It is easy to verify statement (1). For this purpose, consider a new life table where the probability q_1 is

$$q_1 = k\,q = k - k\,e^{-\frac{1}{e(o)}} \tag{2}$$

Then the new probability q_1 is also

$$q_1 = 1 - e^{-\frac{1}{e_1(o)}}$$

where $e_1(o)$ is the expectation for the new table.

If $e(o)$ is sufficiently large compared to the unit of time for which we calculate the probability q, we have, in first approximation

$$q = 1 - \left(1 - \frac{1}{e(o)}\right) = \frac{1}{e(o)}$$

and, in the same way,

$$q_1 = \frac{1}{e_1(o)}$$

The new expectation of life $e_1(o)$ is related by virtue of (2) to the previous expectation of life $e(o)$ by

$$\frac{1}{e_1(o)} = \frac{k}{e(o)}$$

which is equation (1) stated before.

For such a life table, a multiplication by a factor k of the probability q of dying within the unit from age x to $x+1$ leads to an expectation of life which is the prior expectation divided by k. Such life tables exist within the atomic world, since the decrease of the number of radioactive atoms with time follows the exponential function, and the probability of disintegrating is independent of the age.

However, the human life table does not follow the exponential law, since the probabilities, q_x, depend upon the age. Consequently, the proportionality cannot be expected to hold for human life tables.

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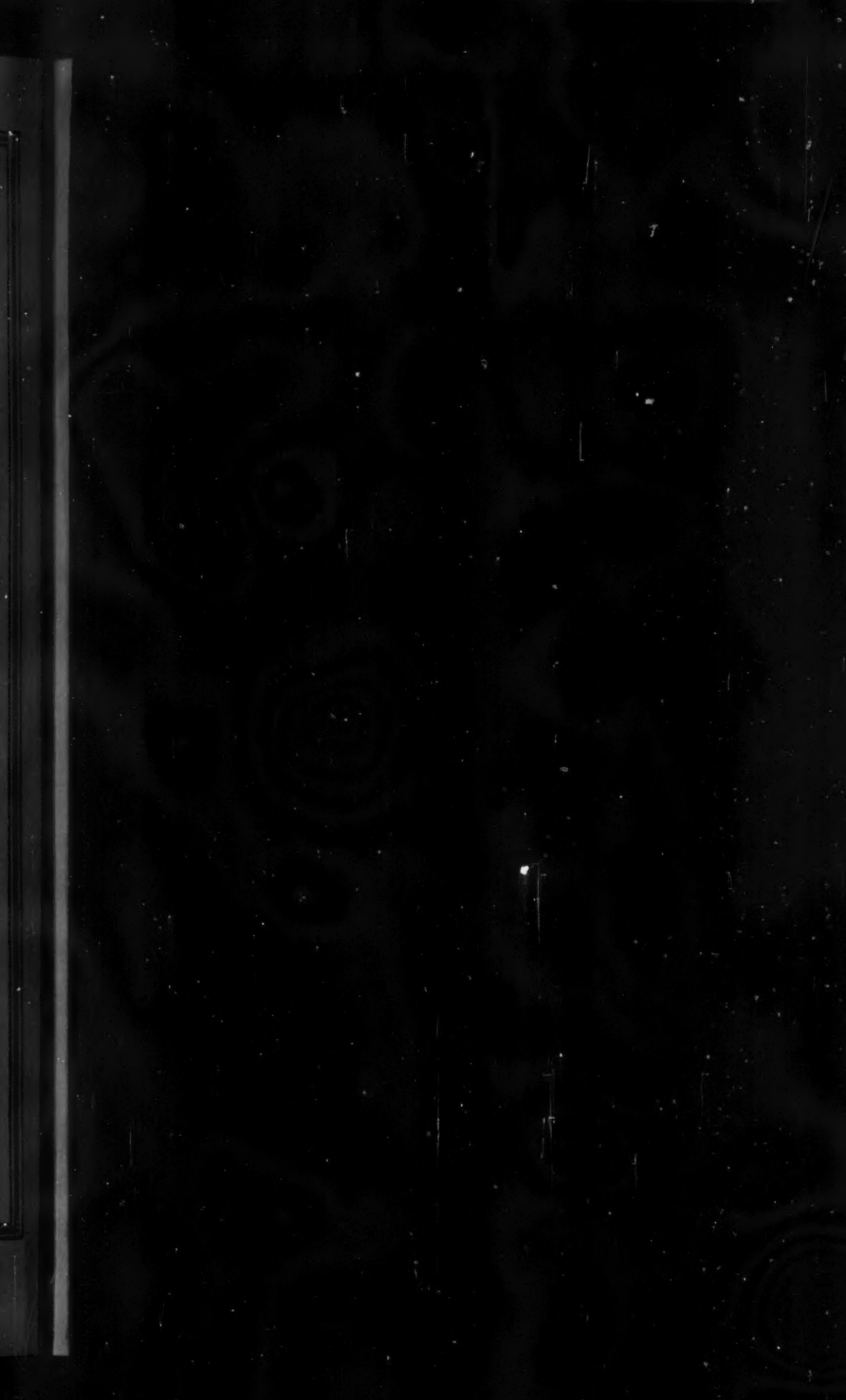
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BALTIMORE—18, MARYLAND, U. S. A.